Rhodium-Catalyzed Carbon−Carbon Bond Forming Reactions of Organometallic Compounds

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1. Introduction

In the past 20 years there has been dramatic growth in the use of transition metal catalysts in synthetically important organic transformations. Recently, increased attention has been paid to rhodium catalysts in the formation of carbon−carbon bonds. In addition to showing new and complementary reactivity to other catalyst systems, rhodium catalysis may permit the development of more environmentally benign processes. This is because the reactions can frequently be performed in the presence of water or even in water as the exclusive solvent. This review discusses the development of new rhodium-catalyzed carbon−carbon bond forming processes using organometallic reagents.

The carbon−carbon bond lies at the heart of organic chemistry, and our ability to synthesize new and interesting organic molecules is inextricably linked to the discovery of new methods that achieve this objective. In recent years, organic chemists have increasingly employed transition metal catalysts as instruments for C−C bond forming processes. The prevalence of these reactions is illustrated by the many processes involving palladium that bear the names of those who discovered them. These include the Kumada-Corriu,[1] Mirozoki-Heck,[2] Stille,[3] Suzuki-Miyaura,[4] Sonogashira,[5] Hiyama,[6] and Tsuji-Trost[7] reactions that permit the cross-coupling of substrates in ways that would have previously been thought impossible.[8] Increasingly, the application of these reactions is becoming a cornerstone in the efficient construction of complex organic molecules.

Due to the tremendous versatility and utility of palladium in the formation of C−C bonds, much effort has been devoted to the development of new reactions with novel applications continuing to be reported. In the past five years, there has been a renewed focus on rhodium catalysts within the context of C−C bond forming reactions. Pertinent to this review, rhodium catalysts have recently been used with organometallic reagents in the formation of new C−C bonds. From a synthetic perspective, these reactions can couple common reagents in ways that have not been demonstrated with other metal catalysts. Many of the new reactions that are catalyzed by rhodium complexes show promise from an environmental perspective since water can be used as a cosolvent or the sole solvent in many cases. Rhodium has also found use in C−C bond forming

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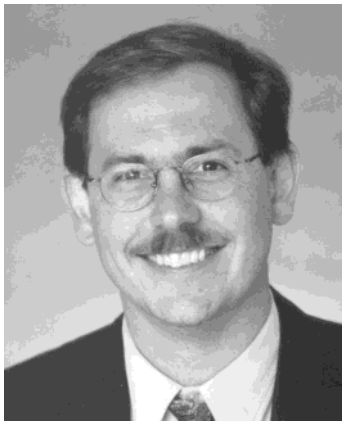
Keith Fagnou was born in Saskatoon, Saskatchewan, Canada in 1971. He received a Bachelor of Education (B.Ed.) degree with distinction from the University of Saskatchewan in 1995 and, after teaching at the high school level for a short period, continued his studies in chemistry at the University of Toronto. In 2000, he received his M.Sc. degree and in 2002 completed a Ph.D. under the supervision of Mark Lautens where his work focused on the discovery of new rhodium catalyzed carbon–carbon and carbon–heteroatom bond forming processes. He has been the recipient of an NSERC Industrial Postgraduate Scholarship in collaboration with AstraZeneca Montreal (M.Sc.), an NSERC Postgraduate Scholarship (Ph.D.), and an NSERC Postdoctoral Fellowship, which was declined in favor of joining the faculty at the University of Ottawa as an assistant professor. His current research interests include the synthesis of novel organometallic complexes to serve as catalysts for organic transformations and the development of new multicomponent coupling reactions.



Mark Lautens was born in Hamilton, Ontario, Canada in 1959. He received his B.Sc. (Distinction) at the University of Guelph in 1981 and his Ph.D. from the University of Wisconsin-Madison in 1985 with Barry M. Trost where he discovered molybdenum catalysts for allylic alkylation and the palladium (II) enyne cyclization. He was an NSERC Postdoctoral Fellow with David A. Evans at Harvard University from 1985 to 1987 prior to taking a position at the University of Toronto, where he now holds the AstraZeneca Chair in Organic Synthesis. He has been Visiting Professor in Paris VI, Marburg, Geneva, Barcelona, and the Max Planck Institute für Kohlenforschung in Mülheim. His awards include an Alfred P. Sloan Fellowship, Eli Lilly Granteeship, Rutherford Memorial Medal from the Royal Society of Canada, E. W. R. Steacie Fellowship from NSERC, and most recently he was elected a Fellow of the Royal Society of Canada (FRSC). His research interests include the development of new reactions using metal catalysts and asymmetric synthesis. He has published 140 manuscripts along with co-workers since his arrival in Toronto.

reactions that do not employ organometallic reagents. Notable examples include rhodium-catalyzed cycloadditions,[9] hydroacylation reacions,[10] and allylic functionalizations.[11] While these reactions illustrate the breadth of reactions that rhodium will mediate, they fall beyond the scope of this review and will not be covered.

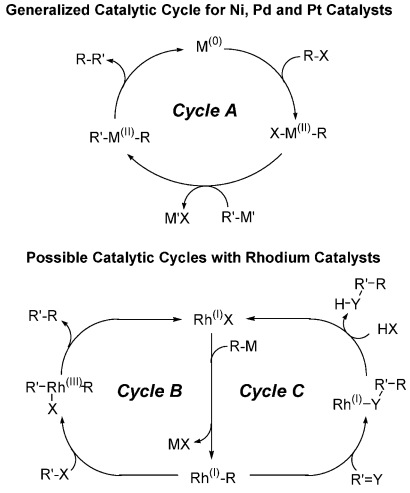
This review has been divided into two main sections: stoichiometric and catalytic processes. Stoichiometric processes will be discussed first to understand how organometallics interact with rhodium complexes. Since most of the catalytic reactions that have emerged in recent years involve the application of aryl organometallics, they will be a primary focus. In the second section, the catalytic reactions of rhodium with organometallics are discussed. This section has been further divided into four subsections: 1,4-additions to activated alkenes, 1,2-addition reactions to carbonyl and imine compounds, additions to unactivated alkenes and alkynes, and reactions for the synthesis of dienes, biaryls, and carbonyl compounds. One review of this chemistry has appeared which is a personal account by Hayashi highlighting the contributions of the Kyoto group.[12] The emphasis in Hayashi's review is on enantioselective additions of organoboranes to activated alkenes and can serve as an introduction to this aspect of the chemistry. The present review will cover chemistry involving organoboranes, stannanes, silanes, bismuthanes, and mercurials with rhodium catalysis that can be used in the formation of carbon−carbon bonds.

2. New Catalytic Possibilities

Compared to the commonly used nickel, palladium, and platinum catalysts, rhodium presents the chemist with new and interesting catalytic possibilities. This becomes clear when generalized catalytic cycles are compared. For example, nickel, palladium, and platinum typically operate within catalytic cycles shuttling between the (0) and (II) oxidation states. As a consequence, transmetalation can only occur with the metal(II) species. To design viable reactions, a suitable electrophilic component must be incorporated that will oxidatively add to the metal(0) complex to produce the organometal(II) species. An organometallic component must be selected that will then undergo transmetalation with the metal(II) complex and subsequently reductively couple with the electrophile. The result is a catalytic cycle illustrated in Scheme 1 as cycle A.

In contrast to group 10 metals, rhodium typically shuttles between the (I) and (III) oxidation states in

Scheme 1



catalytic reactions with organometallics. As a consequence, transmetalation can theoretically occur at two points in the catalytic cycle. Instead of requiring an electrophile that will oxidize the metal in the early stages of the catalytic cycle, transmetalation can occur with rhodium(I) to generate an organorhodium(I) complex capable of reacting in new ways. Since oxidative addition is still a viable pathway, addition of a suitable electrophile will produce a catalytic cycle illustrated as cycle B (which can be described as a "front loaded" version of cycle A with respect to the organometallic). Alternatively, the organorhodium complex can be coupled with units of unsaturation in organic compounds as illustrated in cycle C. This possibility takes advantage of the protic lability of rhodium−heteroatom and rhodium−carbon bonds. The outcome of cycle C is a net R,H-addition across the unsaturated unit.

These mechanistic alternatives are featured throughout this review and have been used to explain many rhodium-catalyzed reactions with organometallics. Through a better appreciation of the subtleties of each step in the catalytic sequence, new transformations will likely be devised.

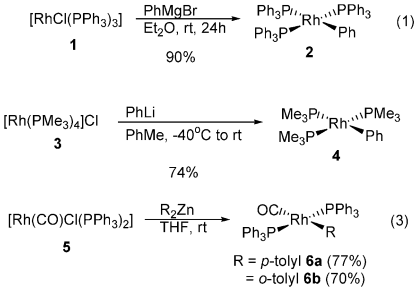
3. Stoichiometric Reactions

The foundation of the catalytic processes described in Scheme 1 is the ability of several organometallics to undergo transmetalation with rhodium(I) and rhodium(III) complexes. Such processes have been documented in stoichiometric reactions and assist in understanding how rhodium can behave catalytically. In Scheme 1, the newly generated organorhodium complex, Rh−R, is proposed to react both by oxidative insertion of suitable electrophiles and by the insertion of unsaturated species into the rhodium−carbon bond. Both of these types of reactivity have been documented in stoichiometric reactions with organorhodium complexes.

3.1 Reactions of Organometallics with Rhodium Complexes

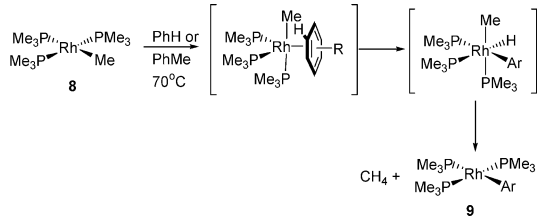
It has long been known that a wide variety of organometallic compounds will react with rhodium(I) halides to generate new organorhodium complexes.[13] In 1968, Keim reported that treatment of $[RhCl(PPh_3)_3]$ **1** with phenylmagnesium bromide gives **2** in 90% yield as a yellow solid (eq 1).[14] The analogous trimethylphosphine complex has also been prepared by the addition of phenyllithium to a solution of $[Rh(PMe_3)_4]Cl$ **3** in toluene at −40 °C. After filtration, **4** was obtained as crystals suitable for X-ray analysis by recrystalization from hexanes (eq 2).[22] Krug and Hartwig recently reported that carbonyl−rhodium aryl complexes **6a**,**b** can be prepared by treatment of $[Rh(CO)Cl(PPh_3)_2]$ **5** with diarylzinc nucleophiles in THF (eq 3).[23]

The choice of solvent can be very important in these reactions as illustrated by the reaction between $[RhCl(PMe_3)_3]$ **7** and methyllithium in refluxing toluene. Instead of forming the expected methyl rhodium species **8**, the tolyl rhodium complex **9** was



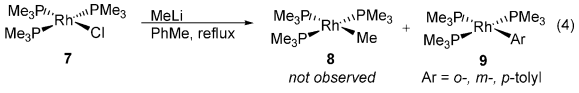
produced as a mixture of *ortho*-, *meta*-, and *para*-isomers.[15] The authors proposed that under these conditions, metalation of the solvent was occurring faster than transmetalation with rhodium. The resulting lithiotoluene could then go on to react with the rhodium chloride complex and produce the observed product. Another explanation was later put forward by Andersen and co-workers.[16] They propose that a C−H activation process is likely responsible for the reaction outcome. To support this claim, $[RhMe(PMe_3)_3]$ **8** was heated at 70 °C in toluene. Under these conditions, the tolyl complex **9** was produced along with methane gas. When the reaction is run in toluene-d_8, CH_3D is produced (Scheme 2).

Scheme 2



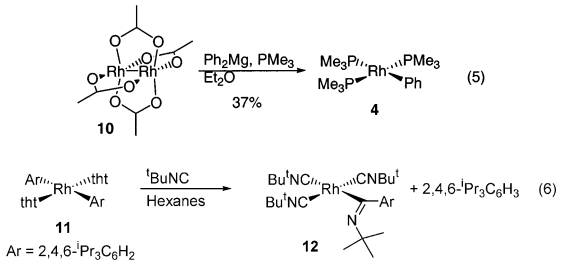
These results are consistent with a mechanism involving the formation of an η^2-arene complex followed by oxidative insertion into an aryl C−H bond. Reductive elimination of methane will give the observed arylrhodium complex **9**. Heating the rhodium−aryl complexes in aromatic solvents does not result in arene metathesis indicating that the rhodium−arene species are less reactive toward oxidative insertion.

While most rhodium−aryl complexes have been prepared by transmetalation with rhodium(I) precursors, rhodium(II) complexes have also been employed. For example, treatment of $[Rh_2(CO_2Me)_4]$ **10** with diphenylmagnesium and trimethylphosphine produces **4** in 37% yield (eq 5).[24] A single electron



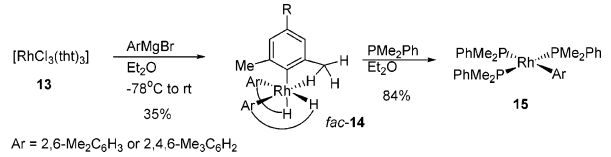
reduction with generation of a phenyl radical may be occurring. An analogous pathway has been proposed in the reaction of $[Rh(2,4,6\text{-}^iPr_3C_6H_2)(tht)_2]$ **11** with 4 equiv of *tert*-butylisocyanide. The product **12** is a rhodium(I) complex where one of the aryl groups has added to an isocyanide ligand (eq 6). When the reaction is run in toluene-d_8, generation of deuterated triisopropylbenzene is observed indi-

cating the intermediacy of a triisopropylbenzene radical that has abstracted deuterium from a solvent molecule.[19]



Rhodium(III) aryl complexes have also been prepared and characterized. In a manner similar to that observed with rhodium(I) halides, rhodium(III) chloride will undergo ligand exchange with a variety of organometallic reagents. For example, $[RhCl_3(tht)_3]$ **13** will react with aryl Grignard reagents to give trisaryl complexes **14** (Scheme 3). Interestingly, they

Scheme 3

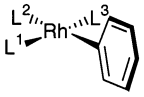


were found to possess a quasi-octahedral coordination geometry with three σ-bound arene ligands situated in a *fac* configuration and the three other coordination sites occupied by agostic interactions to hydrogen atoms on the *ortho* methyl groups of the arenes.[17,19] When less sterically hindered arenes were used, isolation of the rhodium(III) arene complexes was not possible due to solvation. Tris arene complexes can be reduced in the presence of phosphine ligands to generate the tris(phosphine)aryl rhodium(I) complexes. For example, treatment of *fac*-**14** with an excess of PMe_2Ph gives **15** in 84% yield after recrystalization.[19]

3.2 Structural Properties of Aryl–Rhodium Complexes

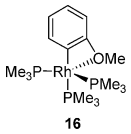
Several crystal structures of rhodium−aryl complexes have been obtained with a diverse range of ancillary ligands. A common structural feature is the orientation of the aryl ring orthogonal to the square plane of the complex that minimizes the steric interactions between the arene and the adjacent ligands. As a result, *ortho*-substituents on the arene will be situated above and below the square plane and block the vacant coordination sites. This property may impede or retard the rate of associative ligand processes with these complexes when bulky *ortho* substituents are present. When an *ortho*-substituent bearing lone pair electrons is present, bidentate binding of the arene becomes possible. For example, complex **16** is proposed to possess a trigonal bipyramidal structure as a result of the *ortho*-methoxy group binding to the rhodium metal.[24] This mode of

Table 1. Rhodium−Aryl Complexes Characterized Crystallographically



L^1	L^2	L^3	aryl	ref
$P(OMe)_3$	$P(OMe)_3$	PPh_3	2,4,6-$Me_3C_6H_2$	18
$P(OMe)_3$	$P(OMe)_3$	$P(OMe)_3$	2,4,6-$Me_3C_6H_2$	18
PMe_2Ph	PMe_2Ph	PMe_2Ph	2,4,6-$Me_3C_6H_2$	19
PMe_3	CO	PMe_3	C_6H_5	20
nbd	nbd	PPh_3	2,6-$Me_2C_6H_3$	21
PMe_3	PMe_3	PMe_3	C_6H_5	22
PPh_3	CO	PPh_3	4-MeC_6H_4	23

binding imparts higher air and thermal stablility to **16** compared to the phenyl analogue **4**.

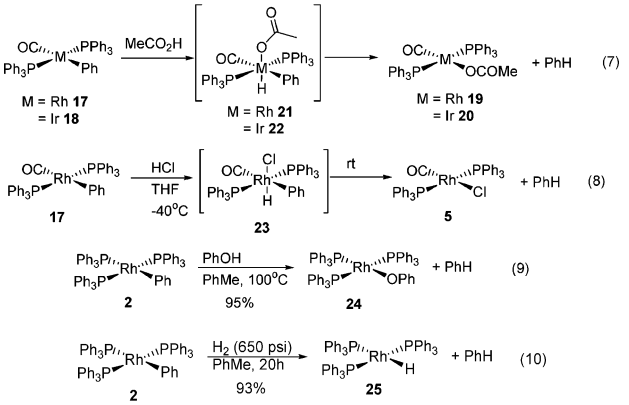


3.3 Reactions of Aryl Rhodium(I) Complexes

3.3.1 Protolytic Cleavage of the Rhodium–Carbon Bond

A common side reaction in nearly all of the rhodium-catalyzed carbon−carbon bond forming reactions is the catalytic demetalation of the organometallic component due in part to the use of protic media. Relevant to the discussion here, these demetalations are catalyzed by the rhodium metal and occur because the aryl−rhodium bond can be more sensitive to protonolysis than the original organometallic compound from which it is derived. Insight into the mechanism of these side processes can be gained by an examination of stoichiometric reactions of rhodium−aryl complexes with a variety of protic compounds.

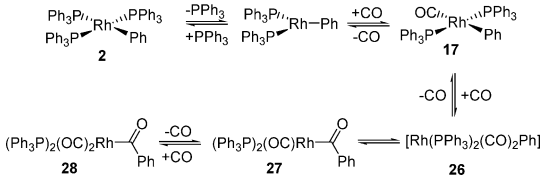
Vaska-type phenyl complexes **17** and **18** have been shown to react with acetic acid to generate benzene and rhodium/iridium(I) acetate complexes **19**/**20**. While no species arising from oxidative addition of the acetic acid O−H could be isolated when M = Rh, isolation of the acetylhydridophenyliridium(III) complex **22** is possible (eq 7).[25] Analogously, treatment of the rhodium phenyl complex **17** with hydrochloric acid lead to the same protolytic cleavage of the rhodium−carbon bond to generate benzene and the rhodium chloride complex **5**. In this case, the octahedral rhodium(III) species **23** arising from oxidative addition of HCl could be detected spectroscopically at −40 °C (eq 8).[20] The same process is observed when **2** is treated with phenol in toluene at 100 °C, indicating that this process can occur with a wide range of O−H bonds (eq 9).[26] An oxidative addition/reductive elimination process has been observed with rhodium−hydride complexes and water (or D_2O) which has been applied to the deuteration of aromatic hydrocarbons.[27,28] Hydrogen has also been used to cleave the rhodium−carbon bond in these complexes. For example, treatment of **2** with 650 psi hydrogen in toluene at 0 °C lead to the generation of rhodium-hydride **25** and benzene in 93% yield (eq 10).[26]



3.3.2 Migratory Insertion Reactions of the Rhodium-Aryl Moiety

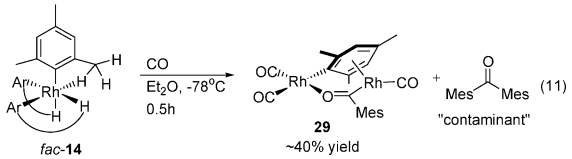
In 1969, Keim reported that exposure of aryl–rhodium complex **2** to an atmosphere of carbon monoxide at −40 °C provides carbonyl complex **17**.[29] Monitoring the reaction by IR revealed the presence of other carbonyl-containing species. At −20 °C, it was determined that **2** reacts with 2 equiv of CO to form the pentacoordinate, dicarbonyl **26** (Scheme 4).

Scheme 4



On warming of the sample to room temperature, a new complex with an IR band in the carbonyl region could be detected, indicating that CO had inserted into the Rh–C bond to give **27**. Reversible coordination of an additional CO ligand generates **28**. The authors noted that all attempts to isolate **27** failed, providing only **17**. Since rhodium is known to mediate and catalyze decarbonylation reactions,[30−34] removal of the CO atmosphere likely leads to decarbonylation and regeneration of **17**.

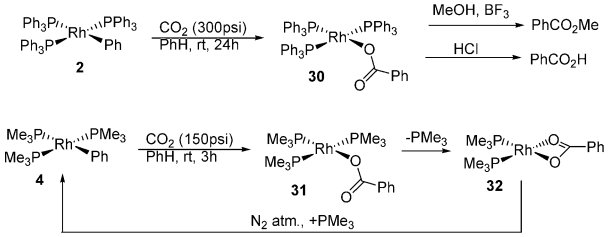
In 1991, Wilkinson and co-workers reported that the tris-aryl rhodium(III) complex **14** reacts rapidly with CO in an ether solution at −78 °C to give the bimetallic carbonyl complex **29** (eq 11).[19] Both metals were assigned an oxidation state of +1, and one of the rhodium atoms bears an acyl ligand arising from insertion of CO into the Rh–C bond. Interestingly, the authors report the generation of dimesityl ketone as a contaminant indicating that a reductive elimination of the acyl and aryl ligands had occurred from an intermediate rhodium(III) complex.



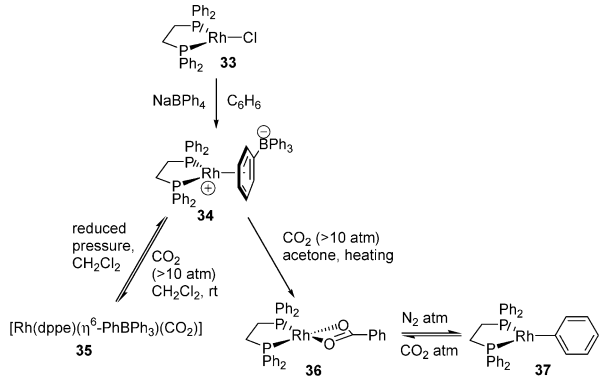
Insertion of carbon dioxide has also been demonstrated with these complexes. In 1974, Vol'pin reported that exposure of a benzene solution of **2** to CO_2 led to the clean formation of a rhodium–benzoate complex **30**.[35] Treatment of **30** with MeOH and boron trifluoride generates the methyl ester while the action of hydrochloric acid gives benzoic acid. It was later found that the trimethylphosphine complex **4** is considerably more reactive than the triphenylphosphine complex **2**. Whereas complete conversion of **2** requires 300 psi CO_2 and 24 h, **4** is consumed in under 3 h at only 150 psi.[22] In situ monitoring revealed that upon formation of **31**, a subsequent displacement of one of the PMe_3 ligands by the acyl oxygen occurs to form **32**. In contrast to the stablility of the tris(triphenylphosphine) rhodium benzoate **30**, bis(trimethylphosphine) rhodium benzoate **32** is unstable in the absence of a CO_2 atmosphere. Upon removal of the CO_2 atmosphere, **32** extrudes CO_2 and reverts to the starting complex **4**.

In 1980, Aresta reported a CO_2 insertion reaction that sheds light on the transmetalation process between rhodium complexes and arylorganometallics.[36] When [Rh(dppe)Cl] **33** is treated with sodium tetraphenylborate, complex **34** is obtained (Scheme 6). Interestingly, X-ray crystallographic analysis

Scheme 5



Scheme 6

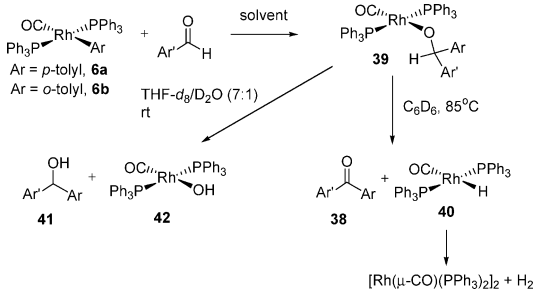


revealed that the Ph_4BNa ligand is bound η^6 through one of the phenyl rings. When **34** is exposed to greater than 10 atm of CO_2 in dichloromethane, a new CO_2 adduct is detected in solution which was assigned to be [Rh(dppe)(η^6-PhBPh$_3$)(CO_2) **35**. Under reduced pressure, loss of CO_2 occurs to regenerate the starting complex **34**. When **34** is subjected to CO_2 and heated in acetone, a new complex is formed bearing a benzoate ligand **36**. For this complex to arise, transmetalation of a phenyl group from the tetraphenylborate ligand must have occurred followed by insertion of CO_2. To verify that transmetalation of the Ph_4BNa ligand had occurred, **36** was heated in acetone under a nitrogen atmosphere which resulted in the extrusion of CO_2 and the formation of rhodium phenyl complex **37**. Resubjection of **37** to a CO_2 atmosphere with heating again produces

benzoate **36**. It therefore appears that the η^6-arylborate binding mode may be an important factor in the transmetalation of aryl organometallics with rhodium(I) complexes.

Krug and Hartwig recently examined aldehyde insertion into the rhodium−aryl bond.[23] The outcome of these processes was found to be highly solvent dependent. For example, the reaction of *p*-tolyl rhodium complex **6a** with a variety of aryl aldehydes in C_6D_6 at 85 °C gives diaryl ketone products **38** in typically 50 to 75% yield (Scheme 7). The reaction

Scheme 7



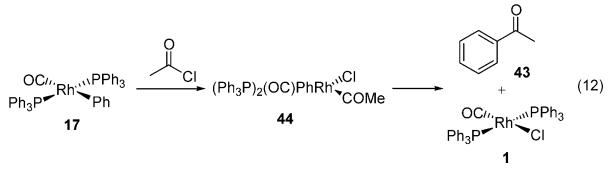
was found to proceed via an initial insertion of the aldehyde into the rhodium−aryl bond to generate rhodium−alkoxide **39**. In C_6D_6, β-hydride elimination occurs to produce the diaryl ketone and a new rhodium−hydride complex **40** which decomposes under the reaction conditions to liberate hydrogen and form $[Rh(\mu\text{-}CO)(PPh_3)_2]_2$. Reaction of *o*-tolyl rhodium species **6b** leads to lower yields and longer reaction times, likely due to the increased bulk of the *ortho* substituent.

When the reaction media is changed to a THF/H_2O mixture, diarylmethanol products **41** are obtained instead of the corresponding diaryl ketones. For example, treatment of **6a** with a variety of aryl aldehydes in THF/H_2O (7:1) at 80 °C generates the diarylmethanol product along with rhodium−hydroxide complex **42**. In protic media, hydrolysis of the intermediate rhodium−alkoxide **39** is faster than β-hydride elimination. Again, *ortho* substitution slows the reaction when **6b** was used.

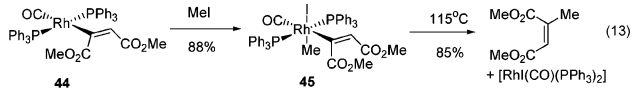
The insertion of styrene into the rhodium−aryl bond has also been documented although the exact reaction conditions were not described. Oi reported that reacting a phenylrhodium complex prepared in situ from reaction of $[Rh(COD)MeCN)_2]$ and $PhSnMe_3$ with styrene gave *trans*-stilbene in 49% yield.[71] A mechanism involving initial insertion of the alkene into the phenyl−rhodium bond followed by β-hydride elimination to regenerate the olefin seems likely.

3.3.3 Carbon–Carbon Bond Forming Processes where Rhodium Undergoes a Change in Oxidation State

A rhodium-mediated alkylation/arylation reaction of carboxylic acid chlorides has been reported by Hegedus. For example, treatment of aryl−rhodium complex **17** with acetyl chloride in THF at −78 °C generates benzophenone **43** in good yield with regeneration of the rhodium−chloride complex **1**.[37,38] Even straight chain alkyl groups could be used under this protocol. The mechanism was proposed to occur via oxidative addition of the acid chloride to give the octahedral rhodium(III) complex **44** followed by reductive elimination of the acyl and aryl ligands (eq 12). The high reactivity of the aryl−rhodium complex toward oxidative addition compared to the corresponding rhodium−chloride is illustrated by the fact that the rhodium−chloride complex is inert toward the acid chlorides under these conditions.



A similar reaction using alkylhalides as the electrophilic component has also been reported. In 1972, Schwartz reported that the vinyl rhodium complex **44** could be reacted with iodomethane to generate the rhodium(III) complex **45** in 88% isolated yield. Heating **45** to 115 °C results in reductive elimination of the vinyl and methyl ligands generating a new carbon−carbon bond with retention of alkene stereochemistry (eq 13).[39]



4. Catalytic Processes

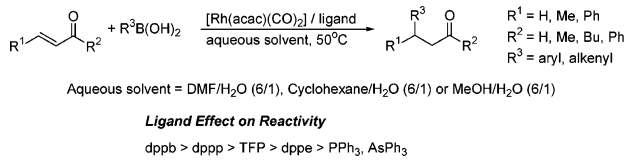
4.1 1,4-Additions to Activated Alkenes

1,4-Conjugate addition of organometallics to activated alkenes is an important process in organic chemistry.[40] The use of metal catalysts in combination with an organometallic reagent has been particularly effective in this regard. Perhaps the most commonly used metal is copper,[41] but reports with other metals have appeared.[42] Frequently, Grignard reagents, organolithiums, or diorganozincs are employed as the organometallic component and while they provide high yields in many cases, issues of chemoselectivity accompany and limit their use. Of particular importance is the search for enantioselective 1,4-addition reactions, and significant advances have been made, particularly with copper catalysts and Grignard or diorganozinc reagents.[43] Success with these reactions typically requires the use of low temperatures and strictly anhydrous reaction conditions. The rhodium-catalyzed reactions presented in this section represent an attractive alternative to these copper-catalyzed additions since they are insensitive to the presence of water, occur under mild conditions, and can be carried out with a wide range of substrates. Furthermore, they employ mild organometallic reagents that are not prone to background reactions and are compatible with aryl nucleophiles that can be problematic with copper catalysis.

4.1.1 Organoboron Nucleophiles

In 1997, Miyaura reported that rhodium(I) complexes will catalyze the 1,4-addition of aryl and

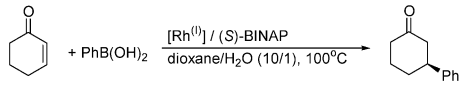
Scheme 8



alkenyl boronic acids to enones in excellent yield.[44] Using [Rh(acac)(CO)$_2$] as the rhodium(I) source, a variety of ligands were examined. Bis(phosphine) ligands possessing large bite angles were shown to give the best results. The authors also noted that the presence of water was required for good reactivity (Scheme 8). The mildness of the reaction conditions was found to avoid aldol condensations of the substrates and products which can be problematic under basic conditions. Even enals selectively undergo 1,4-additions demonstrating the mildness and high chemoselectivity associated with these reactions.

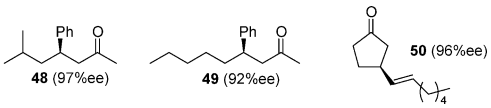
In 1998, Hayashi reported the first enantioselective variant of this transformation.[45] To achieve high yields and enantioselectivity, the solvent was changed to a 10/1 mixture of dioxane and water, the temperature was increased to 100 °C, and the rhodium source was changed from [Rh(acac)(CO)$_2$] to [Rh(acac)(C$_2$H$_4$)$_2$]. The change in rhodium source was done to facilitate the in situ generation of the rhodium−BINAP complex which is slow when the dicarbonyl complex is employed. The benefit of using [Rh(acac)(C$_2$H$_4$)$_2$)] is illustrated in Scheme 9. With

Scheme 9



Entry	Rhodium Complex	Equiv. PhB(OH)$_2$	Yield	Ee
1	[Rh(acac)(CO)$_2$]	1.4	15	43
2	[Rh(acac)(C$_2$H$_4$)$_2$]	1.4	64	97
3	[Rh(acac)((*S*)-BINAP)][a]	1.4	64	97
4	[Rh(acac)(C$_2$H$_4$)$_2$]	2.5	93	97

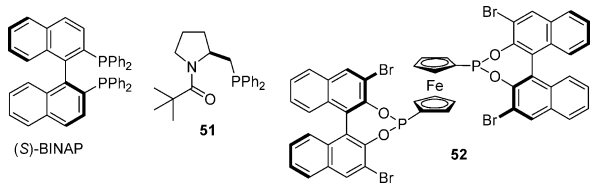
[a] Isolated Rh^{I} BINAP complex used without additional BINAP added *in situ*.



[Rh(acac)(CO$_2$)], **46** reacts with PhB(OH)$_2$ to give **47** in 15% yield and 43% ee (Scheme 9, entry 1). With [Rh(acac)(C$_2$H$_4$)$_2$] as the rhodium source, the yield and ee increase to 64 and 97%, respectively (entry 2). The [Rh(acac)((*S*)-BINAP)] complex was independently prepared, isolated and reacted under otherwise identical reaction conditions giving products in similar yield and enantioselectivity indicating that [Rh(acac)((*S*)-BINAP)] is implicated in the catalytic cycle.

Under these conditions, hydrolytic deboronation of the phenylboronic acid was found to be a competing side reaction. To overcome this problem, an excess of boronic acid was used (entry 4). In some cases, up to 10 equiv of the arylboronic acid is necessary to achieve complete consumption of the alkene. In addition to cyclic enones, acyclic *E*-enones can also be employed (**48**, **49**) as can alkenylboronic acids (**50**).

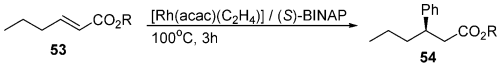
Other chiral ligands have also been employed.[46] Good results have been obtained with the chiral amidomonophosphine ligand **51**[47] and the chiral ferrocenyl bis(phosphinite) ligand **52**.[48]



Hayashi has recently reported that [Rh(OH)(BINAP)]$_2$ is an even more efficient catalyst for these reactions, allowing them to be performed at lower temperatures and with fewer equivalents of arylboronic acid.[60] The reasons for the improved reactivity of the hydroxide catalyst are discussed in section 4.1.2.

Extending these reactions to acrylates revealed that they were much less reactive than the corresponding enones. The nature of the ester substituent was also determined to affect the reactivity. For example, treatment of **53** (R = Me, Et) with 5 equiv of PhB(OH)$_2$ and catalytic [Rh(acac)(C$_2$H$_4$)$_2$]/(*S*)-BINAP in dioxane/water (10/1) at 100 °C leads to complete consumption of starting materials. When R is isopropyl or *tert*-butyl, however, **54** is obtained in only 42 and 21% yields, respectively. The poor results with large ester substituents are a result of competitive deboronation of the phenylboronic acid resulting in consumption of the nucleophile prior to complete reaction of **53**. Changing the nucleophile to a lithium phenylborate species generated in situ from phenyllithium, trimethylborate, and 1 equiv of water gives better results. Use of 2.5 equiv of this nucleophile gives complete consumption of **53** (R = ^{i}Pr) giving **54** in 96% yield and 95% ee (Scheme 10).[49,50]

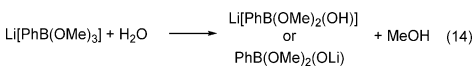
Scheme 10



Conditions (R = ^{i}Pr)	Yield	ee
PhB(OH)$_2$ (5 equiv.) dioxane/H$_2$O (10/1)	42	94
LiPhB(OMe)$_3$/H$_2$O (1/1) 2.5 equiv, dioxane	96	95

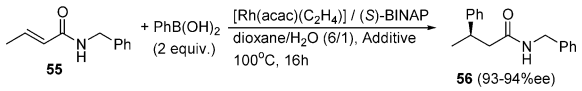
Larger ester groups were also found to provide higher enantioselectivity, albeit at the expense of reactivity. Intriguingly, while the use of lithium arylboronate nucleophiles results in higher yields with the acyclic enoates, best results with cyclic enoates are obtained with simple arylboronic acids.

It is likely that the addition of 1 equiv of water to Li[PhB(OMe)$_3$] generates Li[PhB(OMe)$_2$(OH)] or PhB(OMe)(OLi) plus methanol (eq 14).[51] This is supported by the fact that PhB(OMe)$_2$ does not react with 2-cyclohexenone. When 1 equiv of lithium hydroxide is added, however, the reaction proceeds in quantitative yield.



α,β-Unsaturated amides were also found to suffer from poor reactivity and yields compared to enones. A study on the effects of additives revealed that an aqueous base could be used to obtain complete conversion.[52] For example, reaction of **55** with 2 equiv of $PhB(OH)_2$ and catalytic $[Rh(acac)(C_2H_4)_2]$/(*S*)-BINAP in dioxane/water (6/1) at 100°C for 16 h in the absence of additive generates **56** in only 67% yield (in all cases the enantioselectivity is 93−94%). Addition of even a catalytic amount of acetic acid or hydrochloric acid results in a significant drop in yield (Scheme 11, entries 2 and 3). Addition of boric acid,

Scheme 11



Entry	Additive	Equiv.	Yield
1	none	-	67
2	AcOH	0.05	15
3	HCl	0.05	0
4	$B(OH)_3$	1.0	75
5	Et_3N	2.0	59
6	K_2CO_3	0.05	82
7	KOH	0.05	85

on the other hand, gives a slightly improved yield of 75% (entry 4). The addition of a variety of bases was also examined. Best results were obtained with the addition of catalytic amounts of K_2CO_3 or KOH which provides **56** in 82 and 85% yield, respectively (entries 6 and 7).

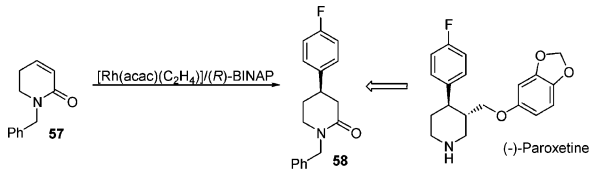
These reactions were found to be general for several crotonamides; crotonamide and its *N*-benzyl, *N*-phenyl, and *N*-cyclohexyl derivatives all give good yields of the adducts in high ee. In contrast, *N*,*N*-disubstituted crotonamides fail to react. It was also determined that electron-deficient arylboronic acids gave faster reactions and higher yields and enantioselectivity.

Interestingly, a reaction that was inhibited by the presence of 5 mol % HCl could be restarted spontaneously by the addition of 15 mol % K_2CO_3. The authors state that the addition of acids or bases will influence the transformation of the Rh(acac) precatalyst into the Rh(OH) catalyst (see section 4.1.2).

For α,β-unsaturated lactams to be employed as substrates in these reactions, slightly modified conditions were required. Relevant to the synthesis of (−)-paroxetine, Hayashi and co-workers envisioned an enantioselective 1,4-addition of a 4-fluorobenzene nucleophile to lactam **57** giving **58** as a useful intermediate.[53] Under the standard conditions used for additions to enones, however, the reaction with **57** and 4-$FC_6H_4B(OH)_2$ gave **58** in only 17% yield with 92% ee (Scheme 12, entry 1). When the same reaction was performed using $PhB(OH)_2$, **58** was isolated in 70% yield (entry 2). The difference in yield was attributed to the instability of the 4-fluorophenyl rhodium(I) intermediate toward protonolysis resulting in consumption of the arylboronic acid prior to complete reaction of **57**.

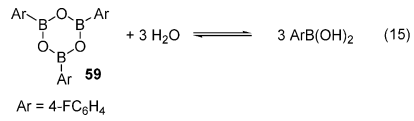
The solution to this problem was 2-fold. Hayashi discovered that by running the reaction at 40 °C instead of 100 °C *and* by using 4-fluorophenylboroxine **59** in combination with only 1 equiv of water

Scheme 12



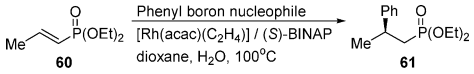
Entry	Arylboron Reagent	Solvent	Temp.(°C)	Yield	Ee
1	4-$FC_6H_4B(OH)_2$	dioxane/water (10/1)	100	17	92
2	$PhB(OH)_2$	dioxane/water (10/1)	100	70	93
3	$(4\text{-}FC_6H_4BO)_3$ **59** / water (1/1)	dioxane	100	36	93
4	$(4\text{-}FC_6H_4BO)_3$ **59** / water (1/1)	dioxane	40	63	97

relative to boron, **58** could be obtained in 63% yield and 97% ee (entry 4). Slightly better yields could be obtained using modified BINAP ligands. Hayashi noted that the use of arylboroxines in combination with 1 equiv of water should theoretically result in the same outcome as using the corresponding arylboronic acid with no water added (eq 15). Regardless, the yields were regularly higher when the boroxine/water mixture was employed.



Compared to other Michael acceptors, alkenylphosphonates have not received the same level of attention in asymmetric catalysis. In 1999, Hayashi reported the first examples of asymmetric additions to these substrates.[54] Using a catalyst generated from $[Rh(acac)(C_2H_4)_2]$ and (*S*)-BINAP, high yields and excellent enantioselectivities could be obtained. With alkenylphosphonate **60**, the typically employed solvent system of dioxane and water (10:1) was found to deactivate the catalyst and provide **61** in only 44% isolated yield and 84% ee (Scheme 13). This catalyst

Scheme 13

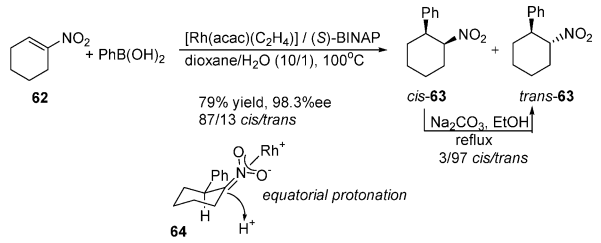


Ph-Boron Nuc.	Quantity H_2O	Yield	ee
$PhB(OH)_2$	10% of solvent	44	84
$(PhBO)_3$	1 equiv. to B	94	96

inactivation was attributed to the large excess of water present in solution. By changing the nucleophile to phenylboroxine, $(PhBO)_3$, and using only 1 equiv of water relative to boron, **61** was generated in 94% yield and 96% ee. The small amount of water was determined to be essential for good conversion, since almost no reaction occurred under anhydrous conditions.

In previous examples, activated alkenes bearing α-substituents were typically not employed due to their low reactivity in these reactions. Recently, Hayashi reported that α-substituted nitroalkenes were good substrates in the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids.[55] Treatment of 1-nitrocyclohexene **62** with 5 equiv of phenylboronic acid and catalytic $[Rh(acac)(C_2H_4)_2]$/(*S*)-BINAP in a dioxane/water mixture (10/1) at 100 °C for 3 h gives **63** in 79% yield as an 87/13 mixture of cis/trans isomers and >98% ee (Scheme 14). The diastereo-

Scheme 14



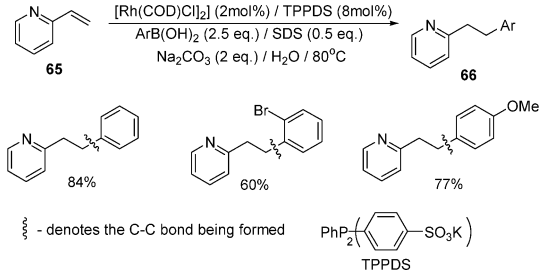
mers can be separated chromatographically or the mixture can be treated with Na_2CO_3 in refluxing ethanol to generate the thermodynamically more stable trans-**63** in a 97/3 trans/cis ratio. The generation of the thermodynamically less stable cis-**63** during the rhodium-catalyzed arylation was attributed to equatorial protonation of rhodium nitronate intermediate **64**.

In all the above examples of rhodium-catalyzed 1,4-addition of organoboronic acids, organic solvents were employed, either alone or as an aqueous mixture. Miyaura has reported that a variety of neutral and cationic rhodium catalysts can be used in the absence of added ligand to achieve conjugate addition of arylboronic acids to α,β-unsaturated ketones, esters, and amides in good yield with water as the only solvent. He also reported that an immobilized catalyst, (hydroxo)rhodium-β-cyclodextrin, is effective in these aqueous reactions.[56]

Hayashi has shown that organobenzodioxaboroles can be used for additions to activated alkenes. Since these can be easily prepared from alkynes and catecholborane, a one-pot hydroboration-asymmetric conjugate addition process is possible.[57] Batey has demonstrated that potassium alkenyl- and aryltrifluoroborates can also be used as substitutes for the boronic acid.[58]

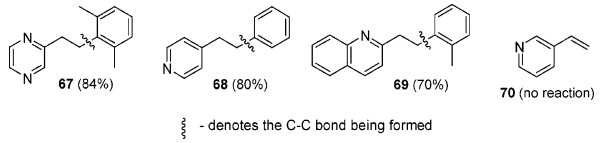
Lautens has demonstrated that certain heteroaromatic alkenes can be used in these reactions.[59] For example, reaction of 2-vinylpyridine **65** with 2.5 equiv of $PhB(OH)_2$ and a catalyst prepared by mixing $[Rh(COD)Cl]_2$ and the water-soluble ligand TPPDS, in the presence of sodium carbonate and SDS as a phase transfer agent in neat water at 80 °C gives the 1,4-addition product **66** in 84% yield. A variety of arylboronic acids were used with similar results (Scheme 15).

Scheme 15



The success of these reactions hinges upon the proper location of the heteroatom within the aromatic ring relative to the alkene. For example, nitrogen heterocycles will react when the nitrogen is located at either the *ortho* or *para* positions, as illustrated

Scheme 16



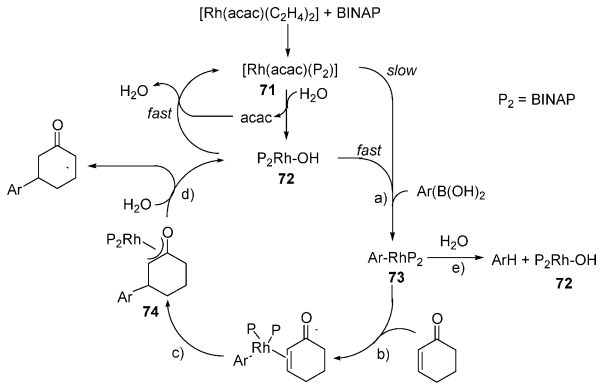
by the successful coupling of 2-vinylpyridine (**66**), 2-vinylpyrazole (**67**), 4-vinylpyridine (**68**), and 2-vinylquinoline (**69**). In contrast to the high reactivity of these substrates, 3-vinylpyridine **70** does not react (Scheme 16).

4.1.2 Detailed Mechanism of 1,4-Addition Reactions with Organoboranes

The catalytic cycle for the 1,4-addition of organoborane reagents to activated alkenes contains steps that are common to many of the reactions discussed in this review. For this reason, the catalytic cycle for 1,4-additions with organoborane nucleophiles is discussed in detail. Detailed mechanistic studies have recently been reported by Hayashi that delineate the important steps in the cycle.[60] An initial overview of the catalytic cycle is provided to give a context for the individual steps and intermediates. Subsequently, the properties of the intermediates and their transformations will be discussed, drawing on experimental support for the proposed pathway.

The catalytic cycle for rhodium-catalyzed 1,4-additions of aryl and alkenylboronic acids to α,β-unsaturated compounds is outlined in Scheme 17

Scheme 17[a]



[a] (a) transmetallation; (b) coordination to the electron-deficient alkene; (c) alkene insertion into Rh−Ar bond; (d) hydrolysis of rhodium-oxo-π-allyl intermediate; (e) hydrolysis of the Rh−C bond.

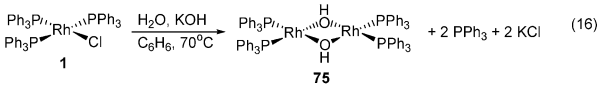
(illustrated for the reaction with cyclohexenone).[60] The precatalyst is typically a bis(phosphine)rhodium(I) complex **71** (usually with a chloride or acac counterion). While transmetalation of the arylboronic acid can occur directly with complex **71**, this process is very slow. Alternatively, the Rh(acac) complex is converted under the reaction conditions to a rhodium hydroxide species **72** that is more reactive toward transmetalation with the organoboronic acid. Transmetalation with **72** will produce a rhodium−aryl complex **73**.

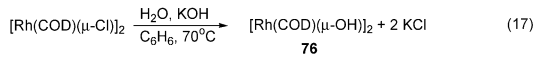
The aryl−rhodium complex **73** can react in two ways under the reaction conditions. An unproductive mode of reactivity is the hydrolysis of the aryl−rhodium bond that reforms the rhodium hydroxide

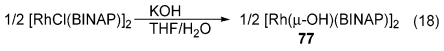
catalyst **72** and gives protonated Ar−H. Alternatively, coordination of the alkene will occur followed by regio- and enantioselective insertion of the alkene into the Rh−C bond. This carborhodation will produce the new carbon−carbon bond and a rhodium-oxa-π-allyl species **74**. Protonolysis of **74** liberates the product and regenerates the rhodium−hydroxide catalyst **72**.

In reactions in which a rhodium hydroxide complex has been used as the rhodium source (i.e., no acac ligand is presence in the reaction mixture), **72** will undergo transmetalation and continue the catalytic cycle. If a rhodium(acac) complex has been used as the precatalyst, the acac ligand remains in the reaction mixture and will have a detrimental effect on the activity of the rhodium catalyst. This is because reaction of the hydroxide species **72** with the acac ligand is very fast, producing the acac complex **71** that becomes a catalyst reservoir. Since transmetalation with **71** is slow, more forcing conditions must be employed to attain efficient turnover.

Evidence for the in situ generation of a rhodium−hydroxide species can be found in stoichiometric and catalytic transformations. It is known, for example, that the bridged hydroxo-complexes **75**[61] and **76**[62] containing either phosphine or olefin ligands can be prepared by treatment of the corresponding chloride with potassium hydroxide in a water/benzene mixture at 70 °C (eqs 16 and 17). Hayashi has shown that treatment of $[RhCl(BINAP)]_2$ with KOH in THF and water generates the hydroxo-bridged complex **77** (eq 18).[60] These conditions are similar to those used for the 1,4-addition reactions. Furthermore, the beneficial effects of base and the inhibitory effects of acid on these reactions lend additional support to this claim.

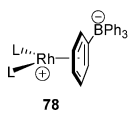






The next step in the catalytic cycle is the transmetalation of the arylboronic acid with the rhodium−hydroxide complex. Ample evidence exists for this step in stoichiometric reactions of rhodium complexes with a variety of organometallics. On the basis of the work of Aresta described in section 3.3.2, transmetalation may proceed via initial coordination of the aryl group to the rhodium in an η^6-fashion. Rhodium(I) $\eta^6-PhBPh_3$ complexes **78** have been prepared with bidentate phosphine ligands,[36] monodentate phosphine and phosphite ligands[63,64] as well as a variety of olefin ligands (Scheme 18).[63]

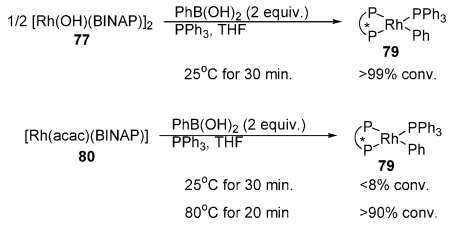
Scheme 18



Ligands (L) = 2 PPh_3, dppe, 2 $P(OMe)_3$, diene, 2 ethylene

It has been demonstrated that transmetalation of arylboronic acids is faster on the rhodium−hydroxide complex than on the corresponding acac species. In stoichiometric reactions, Hayashi found that complete reaction occurs after 30 min at 25 °C when $[Rh(\mu\text{-}OH)(BINAP)]_2$ **77** is reacted with $PhB(OH)_2$ in the presence of PPh_3, to give aryl rhodium(I) complex **79**[60] (Scheme 19). Conversely, less than 8% conversion is

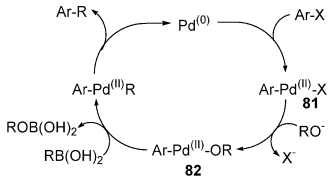
Scheme 19



observed when [Rh(acac)(BINAP)] **80** is reacted under identical conditions. With [Rh(acac)(BINAP)], heating to 80 °C is required for reaction to occur at an appreciable rate.

The enhanced reactivity of the rhodium hydroxide complex may be due in part due to the high oxophilicity of the boron metal. An analogous process has been proposed in the transmetalation of organoboranes to palladium(II) and platinum(II) complexes which are isoelectronic to rhodium(I). While studying palladium-catalyzed cross-coupling reactions of alkenylboranes and alkenylhalides, Suzuki found that the use of phenoxide, alkoxide, and hydroxide bases greatly accelerated the rate of reaction.[65] The rate acceleration was originally attributed to the formation of anionic borates through the coordination of the alkoxide to the boron. Subsequent experiments, however, revealed that the bases were likely reacting at the palladium metal itself to accelerate the rate of transmetalation. These results led Suzuki to propose that the alkoxide or hydroxide bases result in an anion metathesis step in the catalytic cycle (Scheme 20). The aryl palladium(II) halide complex

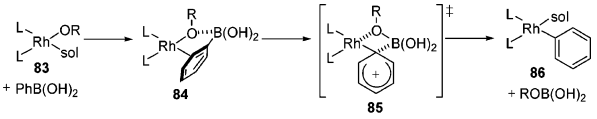
Scheme 20



81, formed by oxidative insertion into the arylhalide bond, will not immediately react with the organoboronic acid, but is first converted to an aryl palladium(II) alkoxide complex **82** that is more reactive to transmetalation. Venanzi has made similar obervations in the reactions of organoboron compounds with platinum(II) disolvento complexes.[66]

A similar transmetalation process can be envisioned for rhodium(I). Commencing with the rhodium hydroxide complex **83**, loss of solvent and coordination of phenylboronic acid to the hydroxide ligand (and potentially η^6 binding through the phenyl ring to the rhodium) produces intermediate **84** (Scheme 21). The transmetalation step could then occur

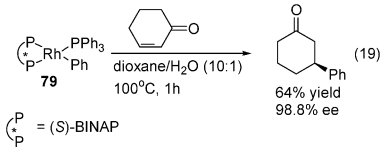
Scheme 21



through **85** to produce the phenylrhodium complex **86** and $(RO)B(OH)_2$.

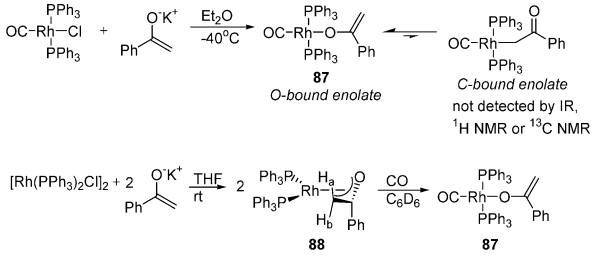
Once generated, the aryl rhodium complex **72** can react in two ways under the reaction conditions (Scheme 17). An uproductive mode of reactivity that is competitive with the productive catalytic cycle is the hydrolysis of the aryl−rhodium bond. This process could occur via water coordination to the rhodium metal and subsequent protonation of the Rh−C bond. Alternatively, water may oxidatively add to the metal creating a hydridohydroxyarylrhodium(III) complex that would reductively eliminate Ar−H. A related oxidative pathway has been documented in stoichiometric reactions of rhodium and iridium with other protic species as well as in the catalytic H/D exchange reactions of arenes (section 3.3.1). In addition to water performing this side reaction, the boronic acids themselves (or other hydroxy containing organometallics) may mediate this process.

To enter the productive catalytic cycle, the aryl rhodium species **73** must first bind the alkene. In addition to making the alkene more electrophilic, the presence of an electron withdrawing group on the olefin favors binding to the electron-rich rhodium(I) metal. Small substituents on the olefin will also favor this step. These trends can account for the fact that a large excess of the arylboronic acid must be employed when the alkene is more sterically encumbered or less activated. Alkene coordination is followed by a regioselective (and enantioselective in the presence of a chiral ligand) insertion of the alkene into the rhodium−carbon bond. Hayashi has verified that a rhodium(I) aryl complex delivers the aryl nucleophile.[60] For example, the stoichiometric reaction of **79** with cyclohexenone generates the 1,4-addition product with the same sense of induction and enantioselectivity as the catalytic reactions (eq 19). Furthermore, **79** was found to react catalytically in the presence of excess cyclohexenone and $PhB(OH)_2$ to give identical results.

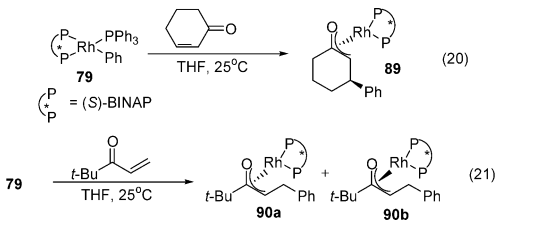


The nucleophlic addition occurs with delivery of the aryl nucleophile to the β-carbon of the alkene and generating a rhodium enolate or an oxa-π-allyl complex **74**. Precedent for the intermediacy and reactivity of these complexes can be found in stoichiometric transformations. For example, Heathcock and co-workers found that treatment of $[Rh(CO)Cl(PPh_3)_2]$ with the potassium enolate of acetophenone in ether at −40 °C generates rhodium-enolate **87** (Scheme 22). Only the O-bound enolate was detected by ^1H and ^{13}C NMR.[67] In another example, Slough and co-workers found that treatment of $[Rh(PPh_3)_2Cl]_2$ with 2 equiv of the potassium enolate of acetophenone in THF at room temperature generates the oxa-π-allyl rhodium complex **88** as determined by NMR.[68,69] When this complex is exposed to a CO atmosphere, it reverts to the η^1-O-bound enolate **87**.

Scheme 22

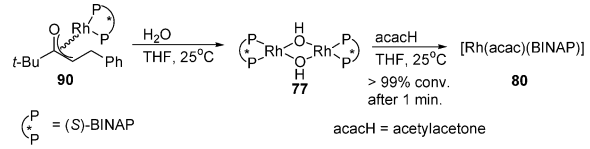


Hayashi found that reaction of phenyl rhodium complex **79** with cyclohexenone under anhydrous conditions in THF at 25 °C generates oxa-π-allyl rhodium complex **89** as one diastereomer based on NMR analysis (eq 20).[60] When the same reaction was performed with *tert*-butylvinyl ketone, a mixture of two diastereomeric oxa-π-allyl rhodium complexes **90a/b** is formed (eq 21).[60] The oxa-π-allyl complex predominates in solution even in the presence of the PPh_3 ligand (which is no longer bound to **89** and **90a/b**). Despite the fact that no O- or C-bound enolates were detected, their intermediacy may still be invoked in hydrolysis or other reactions involving these species.



The next step of interest in the catalytic cycle is product liberation and catalyst regeneration. Protonolysis in a manner similar to that described for the rhodium−aryl complex would liberate the ketone and regenerate the rhodium hydroxide catalyst (Scheme 17). This step has been examined stoichiometrically by hydrolysis of **90** to give the hydroxide-bridged dimer (Scheme 23).[60] When a rhodium(acac) complex

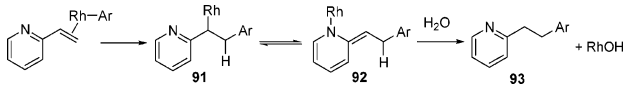
Scheme 23



is used as the rhodium source, the rhodium hydroxide formed upon hydrolysis of the oxa-π-allyl complex may react rapidly with the acetylacetone (acacH) liberated at the beginning of the catalytic cycle (Scheme 17). Evidence for such a process is found by the fast reaction that occurs between the hydroxide dimer and acacH in THF. Sequestering of the rhodium in the form of acac complexes can explain the dramatic increase in rate that is observed when rhodium−hydroxide complexes are used as the rhodium source compared to $[Rh(acac)(L)_2]$ sources.

In the reactions with heteroaromatic alkenes, a similar process may be occurring. It could be argued that coordination of *ortho* nitrogen atom at intermediate **91** will act as the driving force and sufficiently stabilize the complex that hydrolysis of the rhodium−carbon bond is favored. The successful inclusion of 4-vinylpyridine, where such coordination cannot occur, implies that another process may also be important. Tautomerization of intermediate **91** to the rhodium amide **92** could occur followed by protonation to liberate **93** and regenerate the rhodium hydroxide catalyst (Scheme 24).[59] Tautomerization is

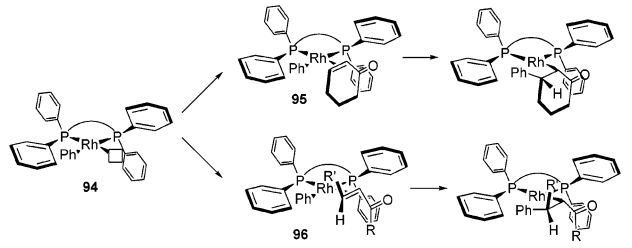
Scheme 24



also possible with 4-vinylpyridine, but not with 3-vinylpyridine, explaining the observed difference in reactivity.

The stereochemical outcome of the enantioselective additions with BINAP as the chiral ligand has been rationalized on the basis of the highly skewed structure known for square planar complexes bound to the BINAP ligand.[70] The (*S*)-BINAP will possess a chiral pocket as illustrated in Scheme 25 where the vacant

Scheme 25

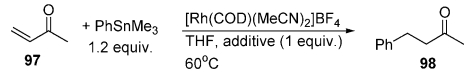


coordination site possesses an open space below and a phenyl group blocking it from above, i.e., **94**. Coordination of cyclohexenone occurs to its 2*si* face, filling the empty space in the lower quadrant as illustrated by complex **95**. Analogously, an (*E*)-enone will coordinate with its 2*re* face producing complex **96**. Migratory insertion will generate the new carbon−carbon bond with the experimentally observed stereochemistry.

4.1.3 Organostannane Nucleophiles

The application of organostannanes in rhodium-catalyzed 1,4-addition reactions was first reported in 1998.[71] Oi and co-workers found that treatment of a variety of enones and enoates with a slight excess of aryl trimethylstannanes (1.2 equiv) and catalytic [Rh(COD)(MeCN)$_2$]BF$_4$ in THF at 60 °C generated the conjugate addition products in good yield. A β-substituent was required on the alkene, otherwise poor yields were obtained (less than 20%). In subsequent studies, it was demonstrated that the use of protic additives enhanced the yields with these difficult substrates.[72] For example, reaction of **97** under anhydrous conditions generated **98** in only 18% yield despite complete consumption of the enone Scheme 26, entry 1). When 1 equiv of methanol or water was

Scheme 26

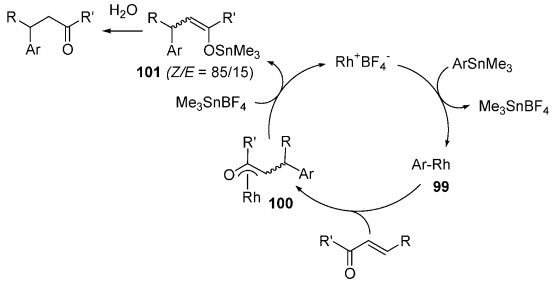


Entry	Additive	Yield
1	none	18
2	AcOH	0
3	MeOH	63
4	H_2O	80

added, the yields increased to 63 and 80%, respectively (entries 3 and 4). Not all protic additives worked equally well, since the use of acetic acid inhibited the reaction completely (entry 2). In addition to aryltrimethylstannanes, Oi examined phenyltributylstannane and tetraphenylstannane and found that they possessed poorer reactivity and gave lower yields. Compared to arylstannanes, alkenylstannanes also showed lower reactivity. Other rhodium catalysts were studied and it was found that the neutral [Rh(COD)Cl]$_2$ complex possessed poorer activity and the addition of phosphine ligands also gave lower yield.[72] While these reactions were initially developed under anhydrous conditions, Li has demonstrated that they can be run in neat water at 50 °C under an air atmosphere demonstrating the robust nature of the catalytic system and the intermediates involved.[73]

To gain mechanistic information, [Rh(COD)(MeCN)$_2$]BF$_4$ was reacted with 1 equiv of phenyltrimethylstannane in THF and D_2O at 25 °C for 25 h.[71] Analysis of the products revealed that the phenylstannane was completely consumed and benzene had been formed. Since it was shown that phenyltrimethylstannane is stable under these conditions, this experiment confirmed that a water-labile species had been generated, which was assigned to be the rhodium(I) phenyl complex. The catalytic reaction is believed to proceed analogously to those with phenylboronic acids (Scheme 27). Thus, transmetalation

Scheme 27



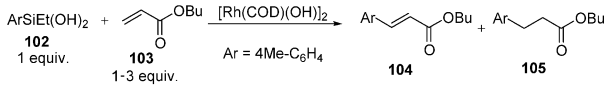
of the arylstannane to the cationic rhodium complex generates the water-sensitive rhodium aryl species **99** and trimethyltin tetrafluoroborate. Conjugate addition generates rhodium enolate **100** which is trapped by the catalytically generated trimethyltin trifluoroborate. The cationic rhodium catalyst is regenerated and the tin enolate **101** is liberated. Production of **101** was evidenced by ^{1}H NMR when the reaction was run in the absence of water. Oi attributes the poor yields obtained with β-unsubstituted substrates in the absence of protic additive to background Michael reaction between the alkene and tin enolate **101**. The addition of protic additives results in the

rapid hydrolysis of these enolates and prevents these side reactions from occurring.

4.1.4 Organosilane Nucleophiles

In 2001, Mori reported that $[Rh(OH)(COD)]_2$ catalyzes the coupling of activated alkenes with aryl silanediols.[74] Of particular interest is the discovery that the outcome of the reaction can be changed from 1,4-addition to a Heck-type addition more typical of palladium catalysis. For example, treatment of (4-methylbenzyl)ethylsilanediol **102** with 3 equiv of **103** and catalytic $[Rh(OH)(COD)]_2$ in anhydrous THF at 70 °C generates the Heck-product **104** in 99% yield (Scheme 28). Conversely, treatment of silanediol **102**

Scheme 28



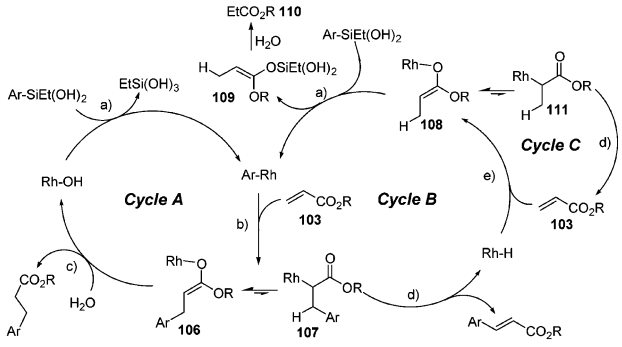
Conditions	Yield 104	Yield 105
THF, 70°C	99[a]	-
THF/H_2O (2/1), 70°C	5	83

[a] Yield is based on the arylsilanediol

with 1 equiv of **103** in a THF/water mixture gives the 1,4-addition product **105** preferentially. A variety of acrylates and acrylamides reacted analogously. It was noted that preference for 1,4-conjugate addition increases when the α,β-unsaturated compound has a more electron-deficient carbonyl group. Thus, reaction of the poorly electron withdrawing *N*,*N*-dimethylacrylamide in aqueous THF results in an almost 1:1 mixture of the Heck and 1,4-addition products.

The proposed mechanism for the 1,4-additions in aqueous THF is analogous to those described for other nucleophiles and is illustrated in Scheme 29

Scheme 29[a]



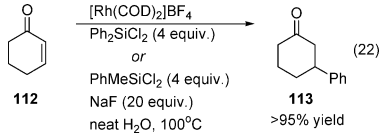
[a] (a) transmetallation; (b) olefin insertion into the Rh-Ar bond (conjugate addition); (c) hydrolysis of the O-bound rhodium enolate; (d) β-hydride elimination; (e) olefin insertion into the Rh−H bond (conjugate reduction).

as cycle A (for the purpose of this discussion, the rhodium oxa-π-allyl intermediates have been drawn as the O- and C-bound enolates). Transmetalation of the aryl silanediol to the rhodium−hydroxide catalyst followed by 1,4-addition and hydrolysis of the O-bound enolate **106** generates the observed product and regenerates the Rh−OH catalyst.

The mechanism of the Heck-type additions deviates from the standard pathway. As with 1,4-addition, transmetalation and addition to the alkene generates the rhodium-enolates **106** and **107** that are likely in equilibrium. Since these reactions are run in the absence of water, enolate hydrolysis does not occur. As a consequence, C-bound enolate **107** undergoes β-hydride elimination to liberate the Heck product and a rhodium−hydride complex (cycle B). This rhodium−hydride complex could then conjugately reduce **103** to give rhodium-enolate **108**. For the catalytic cycle to be reestablished, the authors propose that transmetalation occurs directly at the O-bound enolate **108** to produce the enolsilane **109** and the aryl rhodium species. Enolsilane **109** is protonated on workup producing the experimentally observed reduced ester **110** as a byproduct. One equivalent of the alkene must be consumed to obtain catalyst turnover in this sequence.

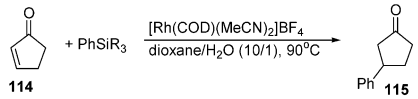
It is possible that a third process is also taking place (cycle C). Since β-hydride elimination will occur on the C-bound enolate in the major pathway, it could also occur with the C-bound enolate **111**. This would simply result in the regeneration of the starting alkene and the rhodium−hydride which will re-enter cycle B. The combination of these three cycles can explain why transmetalation occurs at enolate **108** but *not* at the structurally related enolate **106**. If transmetalation is slow relative to β-hydride elimination, cycle C would become a reservoir for the rhodium catalyst. As a consequence, enolate **108** would be regenerated repetitively until transmetalation with the aryl silanediol eventually occurs.

Li has found that aryl di- and trichlorosilanes can be used as the organometallic component in water as the exclusive solvent when an excess of sodium fluoride is used as an additive.[75] For example, reaction of cyclohexen-2-one **112** with 4 equiv of either diphenyldichlorosilane or phenylmethyldichlorosilane, 20 equiv of NaF and catalytic $[Rh(COD)_2]BF_4$ in water at 100 °C under an air atmosphere generates the conjugate addition product **113** in 97 and 95% yields respectively (eq 22). $[Rh(COD)Cl]_2$ was also found to be an effective catalyst. The authors note that the reaction of $Ph_2Si(OH)_2$ and Ph_2SiCl_2 gave identical results indicating that hydrolysis of the silyl chlorides is likely occurring under the reaction conditions prior to transmetalation. No reaction occurs in the absence of the fluoride additive. The authors propose that the fluoride may produce pentacoordinate silicates that should be more reactive toward transmetalation.



Oi has determined that when organotrialkoxysilanes ($ArSi(OR)_3$) are used as the organometallic reagent under slightly different conditions, fluoride additives are not required.[76] The use of $ArSi(OR)_3$ is particularly advantageous since they are considerably more stable to air and moisture, easy to handle, and easy to prepare. They are also attractive from an environmental perspective since the only byproduct arising from their use is SiO_2. The enhanced reactivity of the trialkoxysilanes is illustrated in

Scheme 30

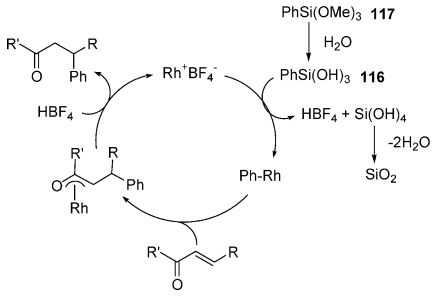


Entry	Silane	Yield
1	$PhSiMe_3$	0
2	$PhSiMe_2(OMe)$	trace
3	$PhSiMe(OMe)_2$	22
4	$PhSi(OMe)_3$	87

Scheme 30. Reaction of **114** with 2 equiv of phenyltrimethylsilane and catalytic $[Rh(COD)(MeCN)_2]BF_4$ in a dioxane/water mixture (10/1) at 90 °C does not lead to the formation of **115** after 20 h (entry 1). As each methyl group is substituted with a methoxy substituent, incrementally improved reactivity is observed. For example, substitution of one of the methyl groups on the silane with a methoxy group gives trace amounts of product (entry 2). The presence of two methoxy groups provides **115** in 22% yield (entry 3), and three gives the best result, generating **115** in 87% after 20 h (entry 4). Fluoride additives were actually found to be detrimental to the reactivity in contrast to the beneficial effects observed with trichlorosilanes. An equimolar amount of potassium hydroxide was also found to inhibit the reactivity as did the use of phosphine ligands. Alkenylsiloxanes reacted analogously.

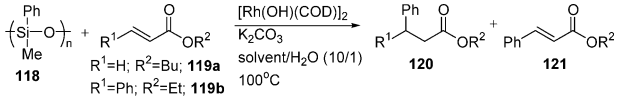
As with the trichlorosilanes, Oi believes that hydrolysis of the trialkoxysilanes to generate silanetriols was likely occurring prior to transmetalation, a proposal supported by the finding that phenylsilanetriol **116** produces identical results to phenyltrimethoxysilane **117**. Mechanistically, hydrolysis of **117** to **116** and transmetalation to the cationic rhodium complex would produce the phenyl rhodium complex, $Si(OH)_4$ and HBF_4. The $Si(OH)_4$ will dehydrate to produce the harmless SiO_2. After addition to the alkene, hydrolysis of the enolate will occur with the catalytically generated HBF_4 to complete the catalytic cycle (Scheme 31).

Scheme 31



Mori has extended the scope of arylsilane nucleophiles to include poly(phenylmethylsiloxane) **118** which is used industrially as a highly thermoresistant silicone oil. The addition of a base was found to be necessary and did not inhibit the reaction in contrast to the inhibition observed when siloxanes were used as reported by Oi. Depending on the substitution pattern on the alkene, different modes of reaction were observed. In cases where no β-substituent is present, the reaction outcome is dependent on the solvent mixture. For example, reaction of **119a** with 3 equiv of silicone (based on Si), catalytic $[Rh(OH)(COD)]_2$ and 1 equiv of potassium carbonate in a dioxane/water mixture gives the 1,4-addition product **120** preferentially (Scheme 32, entry 1). Conversely, in a toluene/water mixture, the Heck product **121** is selectively generated (entry 2). When a β-substituent is present, as with **119b** the 1,4-addition product **120** is obtained exclusively in a toluene/water mixture (entry 3).

Scheme 32



Entry	Solvent	Substrate	Yield 120	Yield 121
1	dioxane/H_2O	**119a**	46	8
2	toluene/H_2O	**119a**	7	35
3	toluene/H_2O	**119b**	49	-

Mori postulates that the role of the base in these reactions is to cleave the polysiloxane into oligosiloxane segments which facilitates the transmetalation step in the catalytic cycle. It is known that treatment of chlorosilanes with aqueous base also generates oligosilanes. Consequently, $PhSiCl_3$, $PhSiMeCl_2$, and $PhSiMe_2Cl$ were subjected to the reaction conditions and were found to react analogously.

4.1.5 Organobismuth Nucleophiles

Li has reported that triphenylbismuth can also be used to carry out these transformations.[77] Treatment of a variety of β-substituted enones and acrylates with approximately 10 equiv of Ph_3Bi and catalytic $[Rh(COD)Cl]_2$ or $[Rh(COD)_2]BF_4$ in water at 50 °C gives the 1,4-addition products in greater than 70% yield. Substrates lacking a β-substituent resulted in significantly lower yields due to the formation of complex product mixtures comprised of mono- and bisphenylation products. Biphenyl is another byproduct in these reactions. The thermal homolytic cleavage of the Bi−Ph bond to generate phenyl radicals likely accounts for both of these side reactions.

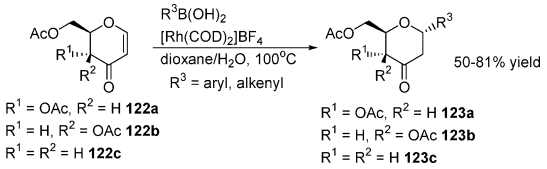
When triphenylbismuth is used, the catalytic cycle is less clear than with other organometallics. Instead of a transmetallative process occurring to generate the rhodium−phenyl species, an oxidative insertion process may in fact occur. This process in known to occur with organophosphorus compounds, and since phosphorus and bismuth are members of the same group, a similar mode of reaction may occur. On the other hand, Li showed that $PhBiBr_2$ does not deliver the aryl group, but when hydrolyzed to the more electron-rich $PhBi(OH)_2$ by the presence of hydroxide base, improved reactivity was observed.[91] This correlation between electron density and reactivity may indicate that the arylbismuth is behaving as a nucleophile and should react via a transmetallative process rather than by oxidative addition.

4.1.6 Application in Organic Synthesis

Maddaford has applied rhodium-catalyzed 1,4-additions to the preparation of C-glycosides.[78] His approach employs enone **122**, which possesses substantially different electronic properties than the

enones previously examined since the presence of the oxygen atom makes the alkene substantially more electron rich. A screening of several rhodium complexes revealed that cationic $[Rh(COD)_2]BF_4$ efficiently catalyzed the diastereoselective addition of a variety of aryl and alkenyl boronic acids to give **123** as one diastereomer in moderate to good yields (Scheme 33). Use of neutral rhodium complexes or

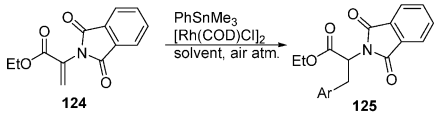
Scheme 33



the addition of phosphines resulted in no reaction. Intriguingly, use of $[Rh(COD)_2]OTf$ (OTf = trifluoromethanesulfonate) also gave no reaction indicating that the counterion may play an important role. Addition of a catalytic amount of potassium hydroxide in conjunction with $[Rh(COD)_2]OTf$ leads to complete reaction within 15 min.

Li has applied the 1,4-addition of aryl and alkenylstannanes to the preparation of α-amino acids.[79] In the course of achieving this goal, he also discovered that sonication of the reaction had a profound effect on the reaction time. Ethyl-α-phthalimidoacrylate was chosen due to its high stability in water and enhanced reactivity with nucleophiles compared to more electron-rich amidoacrylates. Initial experiments revealed that treatment of **124** with 2 equiv of $PhSnMe_3$ in refluxing water overnight gave **125** in 18% yield (Scheme 34, entry 1). No reaction was

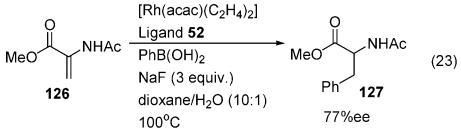
Scheme 34



Entry	Conditions	Yield
1	H_2O, reflux, overnight	18
2	H_2O, rt, overnight	0
3	H_2O, rt, sonication, 2h	82
4	dioxane, rt, sonication, 2h	11

observed at room temperature (entry 2). When the reaction mixture was subjected to sonication at room temperature, however, **125** was isolated in 82% after only 2 h of reaction (entry 3). The benefit of using water as the solvent is illustrated by the fact that performing the reaction in dioxane provides **125** in only 11% after 2 h.

Reetz has performed this reaction enantioselectively using a chiral bis(phosphinite) ligand.[48] Treatment of **126** with $PhB(OH)_2$, sodium fluoride and a catalyst prepared from $[Rh(acac)(C_2H_4)_2]$ and chiral ligand **52** in a dioxane/water mixture at 100°C gave **127** in 77% ee (eq 23). This result is of particular interest since it shows that a chiral center can be created not only by facial selectivity in the addition of the nucleophile to the *β*-carbon, but also by enantioselective protonation of the rhodium-enolate at the α-carbon.



4.2 1,2-Additions to Carbonyls and Imines

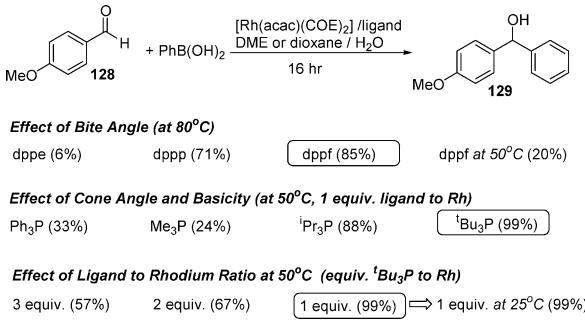
The addition of carbon nucleophiles to carbonyl and heterocarbonyl compounds such as ketones, aldehydes, and imines is a commonly employed strategy in organic synthesis in the formation of carbon−carbon bonds. These reactions are exemplified by Barbier−Grignard type reactions which occur in high yield.[80] The success of these reactions hinges on the protection of sensitive functional groups and the removal of acidic protons from the substrate. While knowledge of protecting group strategies has grown to compensate for such chemoselectivity issues, a more attractive strategy would employ nucleophiles that do not suffer from these issues. As with 1,4-additions, rhodium catalysis has provided chemists with attractive alternatives to the Grignard-type additions that have become commonplace in organic chemistry.

4.2.1 Organoboron Nucleophiles

In 1998, Miyaura reported that rhodium catalyzes the addition of aryl and alkenylboronic acids to aldehydes giving secondary alcohols in good to excellent yields.[81] Optimal conditions were determined to be reaction of the aldehyde with 2 equiv of the boronic acid and a catalyst generated in situ from $[Rh(acac)(CO)_2]$ and dppf in a DME/water mixture at 80 °C. A variety of arylboronic acids and aldehydes could be used. The reactions were facilitated by the presence of an electron withdrawing group on the aldehyde and an electron donating group on the aryboronic acid, suggesting that the mechanism involves a nucleophilic attack of the aryl group on the aldehyde.

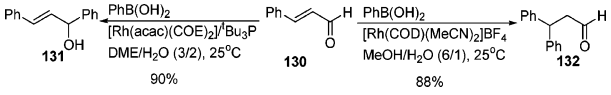
The effect of added ligands was also examined in the addition of phenylboronic acid to 4-methoxybenzaldehyde **128** (Scheme 35).[82] When bisphosphines

Scheme 35



are employed, the reaction is accelerated by ligands with a large P−Rh−P bite angle such as dppf. Monophosphines are also useful if basic trialkylphosphines with large cone angles are employed such as tri-*tert*-butylphosphine. The ligand-to-rhodium ratio is also important, with the best results being obtained when a 1:1 ratio of Rh:^{t}Bu$_3$P is used. Under these conditions, a quantitative yield of **129** can be obtained even at room temperature.

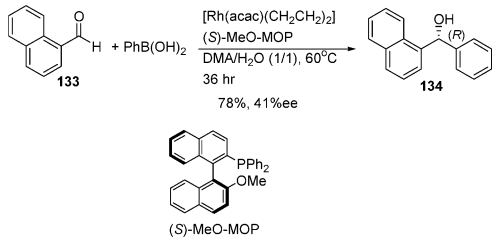
Scheme 36



Proper choice of the rhodium source, added ligands, solvent, and reaction temperature permits the reaction to be directed toward either 1,2- or 1,4-addition as illustrated by reactions with **130** (Scheme 36).[82] Use of a catalyst prepared from $[Rh(acac)(COE)_2]$ and $^tBu_3P$ (1:1 ratio) in a DME/H_2O mixture (3/2) at room temperature gives the 1,2-addition product **131** exclusively in 90% yield. Changing to a cationic rhodium catalyst, $[Rh(COD)(MeCN)_2]BF_4$ in the absence of added ligand and in a methanol/water mixture (6/1) at room temperature gives the 1,4-addition product **132** exclusively. If the temperature is increased to 50 °C, a mixture of both products is produced.

Despite the successful development of highly enantioselective 1,4-additions with a wide range of activated alkenes, only one example of the enantioselective addition of arylboronic acids has been reported with aldehydes. In his initial communication, Miyaura reported that the monodentate (*S*)-MeO-MOP ligand could be used in combination with $[Rh(acac)(C_2H_4)_2]$ to catalyze the addition of $PhB(OH)_2$ to naphthaldehyde **133** giving diarylmethanol **134** in 78% yield and 41% ee (Scheme 37).[81] The bidenate ligands DIOP

Scheme 37

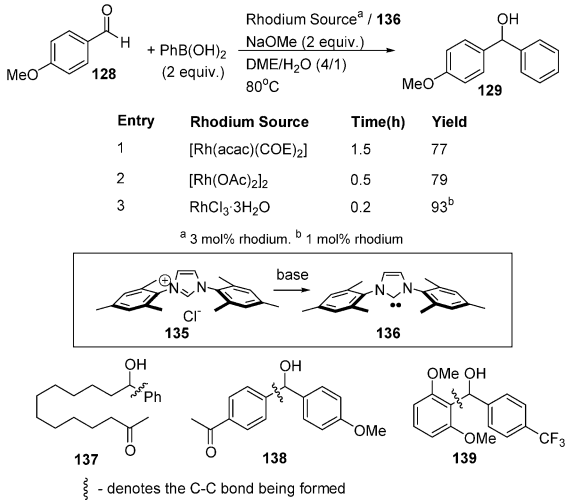


and BINAP gave racemic product.

The finding that these reactions were best run with sterically hindered and strongly basic ligands attracted the attention of Fürstner who subsequently applied *N*-heterocyclic carbene (NHC) ligands,[83] which are known for their strong σ-donor and weak π-acceptor properties.[84,85] The best results were obtained with NHC **136** when generated in situ via deprotonation of **135**. In addition to a variety of rhodium(I) precatalysts, $[Rh(OAc)_2]_2$ and $RhCl_3{\cdot}3H_2O$ could also be employed (Scheme 38, entries 2 and 3). With these precursors, in situ reduction to rhodium(I) is likely occurring. A variety of boronic acids and aldehydes (including aliphatic aldehydes) were successfully coupled using a catalyst generated from $RhCl_3{\cdot}3H_2O$ and **136**. High chemoselectivity was observed for addition to the aldehyde when a ketone functionality was present in either substrate (addition products **137** and **138**). Even very sterically hindered arylboronic acids could be employed as illustrated by the generation of **139** from the addition of 2,6-$(MeO)_2$-$C_6H_3B(OH)_2$.

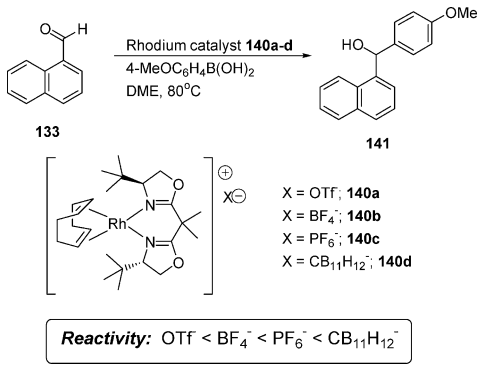
Using ligands with nitrogen donor atoms, Frost has documented a significant counterion effect associated with rhodium-catalyzed additions of arylboronic acids

Scheme 38



to aldehydes. This is illustrated in the reaction of aldehyde **133** with 4-methoxyphenylboronic acid in the presence of cationic rhodium complexes **140a**−**d**. Best results were obtained with the extremely weakly coordinating carborane counterion, indicating that the Lewis acidity of the rhodium catalyst and the ability to activate the aldehyde carbonyl by binding to it are important aspects of the reaction pathway (Scheme 39).[86] As previously observed by

Scheme 39

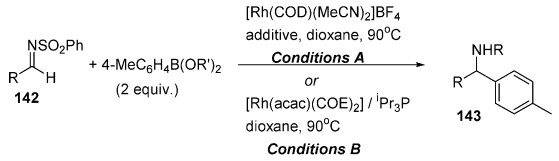


Miyaura, electron-deficient aldehydes and electron-rich arylboronic acids gave the best reactivity. In contrast to previous reports, however, the presence of just 1 equiv of water in the reaction mixture lead to decreased catalyst activity. Optimal solvents were determined to be anhydrous DME or dioxane.

Conditions have also been established for the addition of organoborane reagents to aldimines. Miyaura has reported that cationic rhodium complexes, alone or in the presence of phosphine ligands, catalyze the addition of sodium tetraphenylborate to aromatic aldimines in anhydrous dioxane at 90 °C.[87] The nature of the *N*-substituent was determined to be important to the outcome of the reaction. While less than 10% conversion occurred with *N*-butyl, benzyl, or phenyl aldimines, good outcomes were obtained with *N*-sulfonyl and benzoyl substrates. These results support the notion that the reaction proceeds via a nucleophilic attack of the aryl group on the C═N bond since the best results were observed with electron-deficient aldimines.

While the use of tetraphenylborate generates the amine product in good yield, the lack of readily available functionalized tetraarylborates limits the use of this methodology. With this in mind, Miyaura established conditions under which arylboronic acids and esters could be employed.[88] In addition to high reactivity, *N*-sulfonyl aldimines have the added benefit of increased stability toward hydrolysis which could be problematic in reactions where water is present. Despite the fact that arylboronic acids are known to be in equilibrium with the boroxine, $(ArBO)_3$, and H_2O, no hydrolysis of **142** was observed when reactions were run in anhydrous dioxane at 90 °C. Under these conditions, treatment of **142** with cationic $[Rh(COD)(MeCN)_2]BF_4$ and 2 equiv of 4-tolylboronic acid generated **143** in 99% yield (Scheme 40,

Scheme 40

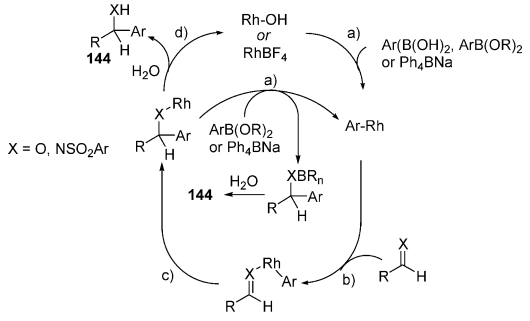


Entry	R Group	OR' Group	Conditions	Yield
1	Phenyl	OH	A (no additive)	99
2	Phenyl	OCH_2CH_2O	A (Et_3N additive)	87
3	(*E*)-CH=CHPh	OH	B	90
4	Cyclohexyl	OH	B	72

entry 1). Alternatively, arylboronic esters can be used in conjunction with triethylamine as an additive (entry 2). Aliphatic imines and α,β-unsaturated imines were also compatible when a catalyst generated from a 1:1 ratio of $[Rh(acac)(COE)_2]$ and $^iPr_3P$ is used (entries 3 and 4).

The mechanism of these reactions contains many of the same elementary processes as the rhodium-catalyzed 1,4-addition reactions (Scheme 41). Com-

Scheme 41[a]



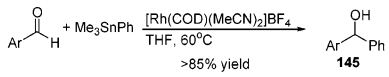
[a] (a) transmetallation; (b) coordination to the C=O; (c) carbonyl insertion into Rh−Ar bond; (d) hydrolysis of rhodium-alkoxide.

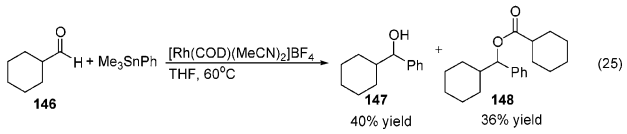
mencing with the rhodium(I) complex, transmetalation will generate the aryl or alkenylrhodium complex. Coordination of the aldehyde or imine is then followed by insertion of the C=O or C=N bond into the rhodium−carbon bond. A rhodium alkoxide or amide bond is formed that may be hydrolyzed before subsequent transmetalation with another arylboronic acid occurs. When arylboronic esters or tetraphenylborate nucleophiles are employed under anhydrous conditions, transmetalation may occur directly with the rhodium alkoxide/amide to produce a new aryl rhodium complex and bypass the Rh−OH species entirely.

Miyaura proposes that there are two opposing factors influencing the rate of addition to the C=O bond.[82] First, the presence of strongly electron donating ligands results in a more electron-rich rhodium center and increased polarization of the rhodium−carbon bond which will result in an increase in the nucleophilicity of the aryl or alkenyl moiety. The second factor is the Lewis acidity of the rhodium metal that is required for efficient transmetalation and coordination of the carbonyl or imine functionality. By using coordinatively unsaturated rhodium catalysts, this property is retained. The use of bulky, electron donating ligands and a low ligand-to-rhodium ratio allows both properties to be maximized.

4.2.2 Organostannane Nucleophiles

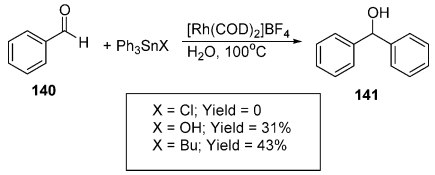
In 1997, Oi reported that cationic rhodium complexes could be used to catalyze the addition of arylstannanes to aldehydes in good yield.[89] Treatment of a variety of aromatic aldehydes with 1.2 equiv of an aryltrimethylstannane and catalytic $[Rh(COD)(MeCN)_2]BF_4$ in THF at 60 °C generates the diarylmethanol products **145** in greater than 85% yield (eq 24). Use of more sterically hindered arylstannanes, such as $PhSnBu_3$ or Ph_4Sn, gave lower yields. Addition of phosphine ligands inhibited the reaction. When aliphatic aldehydes such as cyclohexanecarboxaldehyde **146** were used, the yield of **147** was substantially lower due the production of an ester byproduct **148** (eq 25).





Li has found that these reactions can be performed in neat water at 110 °C with catalytic $[Rh(COD)_2]BF_4$.[90] Aromatic aldehydes react in greater than 70% yield and aliphatic aldehydes in 52 to 65% yield. Li has also reported an electronic effect with respect to the arylstannane in these reactions,[91] which is illustrated in the reaction of benzaldehyde **140** with three different triphenylstannyl reagents (Scheme 42). When Ph_3SnCl is employed, no reaction is

Scheme 42



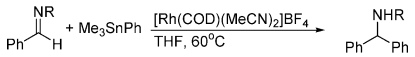
observed. With Ph_3SnOH, benzil **141** is produced in 31% yield, and with Ph_3SnBu **141** is produced in 43% yield. Li attributes these relative yields to the electronic character of the X-group on the stannane.

To appreciate the electronic influence, both inductive and resonance effects must be considered. Both chloride and hydroxide ligands are inductively electron withdrawing and possess lone pair electrons that can donate electron density to the empty d-orbital of the tin metal via resonance. With hydroxide, the donating resonance effect is stronger than the inductive withdrawing effect, so a sufficiently nucleophilic arylstannane is produced to participate in the reaction. On the other hand, the inductive effect dominates with the chlorostannane, so no reaction is observed. Ph_3SnBu is the most nucleophlic and provides the highest yield since only an inductive donating effect is present.

Other influences of the chloride, hydroxyl, and methyl substituents on the reactivity may also be important when the overall catalytic cycle is considered. Importantly, HCl is produced from the partial hydrolysis of the trichlorostannane. Since HCl is known to poison the analogous 1,4-addition reactions with organoboronic acids, its influence in these reactions may be significant. For example, Li determined that the addition of hydroxide promoted reaction with $PhSnCl_3$. This enhanced reactivity with base additives could be attributed to the complete hydrolysis of the stannane to the more electron-rich $PhSn(OH)_3$ or to the generation of ate-complexes. The base could also serve to neutralize the HCl and restart the reaction by removing the acid poison. It is clear that multiple factors influence the catalytic cycle and the individual steps. The electronic effect observed by Li has been seen with other organometallics[92] and will likely be useful in the design of new transformations.

In 1999, Oi reported that aryl and alkenyltrimethylstannanes could be added to a variety of aromatic aldimines with catalytic $[Rh(COD)(MeCN)_2]BF_4$ in refluxing THF. The nature of the *N*-substituent was found to be important to the reactivity. *N*-Toluenesulfonyl imines gave the best results (Scheme 43, entry 1), but good yields could also be obtained with *N*-diethoxyphosphoryl, benzoyl, and tertbutylcarboxyl imines (entries 2−4).

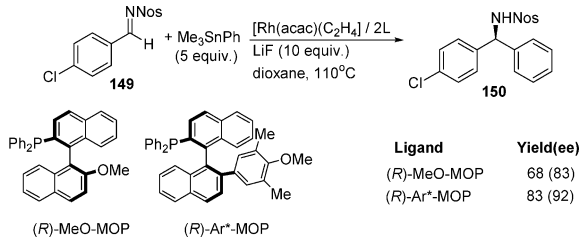
Scheme 43



Entry	R-Group	Yield
1	$SO_2C_6H_4Me$	98
2	$PO(OEt)_2$	84
3	COPh	48
4	$CO_2{}^tBu$	74

Highly enantioselective additions of aryl and alkenylstannanes to imines have been developed by Hayashi using a cationic rhodium catalyst and a chiral monodentate phosphine ligand.[93] *N*-4-Nitrobenzenesulfonylimines (*N*-Nosylimines) gave the best results. For example, treatment of **149** with 5 equiv of $PhSnMe_3$, 10 equiv of lithium fluoride, and a catalytic amount of $[Rh(acac)(C_2H_4)_2]$ and (*R*)-MeO-MOP in dioxane at 110 °C for 12 h generates diarylmethylamine **150** in 68% yield and 83% ee (Scheme 44). While the use of LiF was not necessary, it was found to give more reproducible results.

Scheme 44

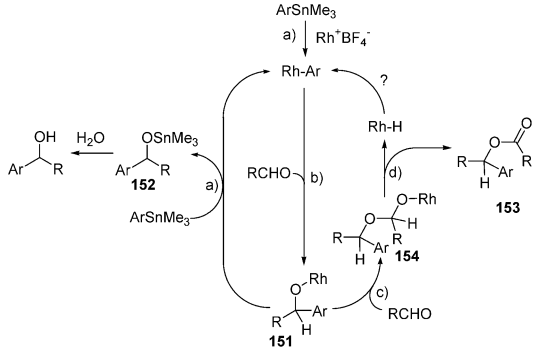


Ligand	Yield(ee)
(*R*)-MeO-MOP	68 (83)
(*R*)-Ar*-MOP	83 (92)

Slightly higher yields and enantioselectivities were obtained using (*R*)-Ar*-MOP as the chiral ligand. With this ligand, **150** can be obtained in 83% yield and 92% ee. Importantly, chelating phosphines caused the arylation reactions to be very slow giving less than 10% yield after 12 h. These reactions can also be applied to the asymmetric 1,2-arylation of α,*β*-unsaturated *N*-nosylaldimines to generate enantioenriched allylamines.[94]

The mechanism for the production of the diarylmethanol products is similar to that with organoboron reagents under anhydrous conditions (Scheme 45). Production of the aryl rhodium complex leads to carbonyl insertion and the production of **151**. Transmetalation will regenerate the aryl rhodium species and alkoxystannane **152** as observed by NMR that is hydrolyzed on workup. When aliphatic aldehydes are used, ester byproducts are produced that most likely arise from carbonyl insertion into the rhodium-alkoxide bond of **151** to give intermediate **154**. *β*-Hydride elimination will liberate **153** and produce a rhodium hydride. It is not known how the Rh−H reenters the catalytic cycle under the anhydrous conditions.

Scheme 45[a]

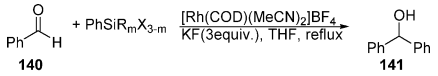


[a] (a) transmetallaton; (b) carbonyl insertion in to Rh−Ar bond; (c) carbonyl insertion into the Rh−OR bond; (d) *β*-H elimination

4.2.3 Organosilane Nucleophiles

The application of organosilane reagents has been examined by Oi.[95] Treatment of benzaldehyde **140** with a variety of phenyl silanes, 3 equiv of potassium fluoride, and catalytic $[Rh(COD)(MeCN)_2]BF_4$ in refluxing THF revealed that the reactions were highly sensitive to the silicon substituents. While $PhSiMe_3$ and $PhSiMe_2F$ did not induce reactions (Scheme 46, entries 1 and 2), $PhSiMeF_2$ reacted to give **141** in 95% yield (entry 3). The presence of three fluoride ligands, as with $PhSiF_3$, proved less reactive. Reactions run in the absence of KF additive gave lower yields.

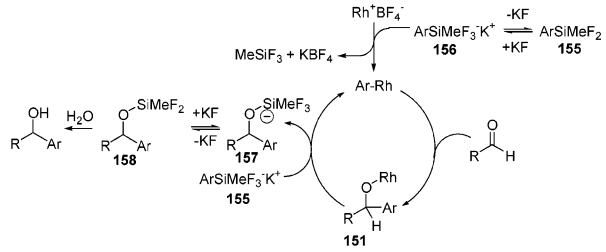
Scheme 46



Entry	Silane	Yield
1	$PhSiMe_3$	0
2	$PhSiMe_2F$	0
3	$PhSiMeF_2$	95
4	$PhSiF_3$	18

The role of the added fluoride is summarized in Scheme 47. Oi proposes that fluoride binding to

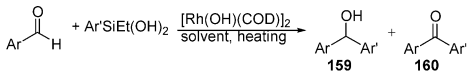
Scheme 47



arylsilane **155** produces silicate **156** which is the active transmetallating species. As described previously, transmetalation and C=O insertion generates **151**, which is proposed to undergo transmetalation directly with another arylsilicate to provide **157**. Loss of fluoride gives silyl ether **158** which upon aqueous workup gives the diarylmethanol product.

Mori has found that when aryl and alkenylsilanediols are used as the nucleophilic component in 1,2-additions, the reaction outcome can be highly dependent on the reaction temperature.[96] For example, reaction of benzaldehyde with 2 equiv of 4-$MeOC_6H_4SiEt(OH)_2$ and catalytic $[Rh(COD)(MeCN)_2]BF_4$ in refluxing THF gives diarylmethanol **159** as the exclusive product in 66% yield (Scheme 48, entry

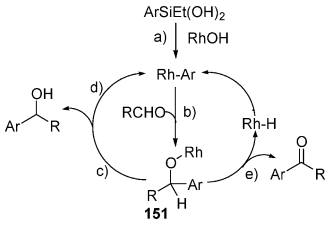
Scheme 48



Entry	Solvent (Temp)	Ar	Ar'	Yield 159	Yield 160
1	THF (70)	4-$MeOC_6H_4$	C_6H_5	66	0
2	dioxane (100)	4-$MeOC_6H_4$	C_6H_5	53	8
3	THF (70)	C_6H_5	4-$MeOC_6H_4$	59	0
4	dioxane (100)	C_6H_5	4-$MeOC_6H_4$	75	6
5	dioxane (100)	4-$MeOC_6H_4$	4-$MeOC_6H_4$	47	23

1). When the reaction temperature is increased to 100 °C in dioxane, a mixture of **159** and diaryl ketone **160** is obtained in 53 and 8% yield, respectively (entry 2). Similar outcomes were observed for 4-methoxybenzaldehyde and $PhSiEt(OH)_2$ (entries 3 and 4). The amount of dirayl ketone is highest when both components possess electron donating groups. For example, reaction of 4-methoxybenzaldehyde and 4-$MeOC_6H_4Si(OH)_2$ in dioxane at 100 °C gives **159** in 47% yield and **160** in 23% yield (entry 5). Conversely, the presence of an electron withdrawing group on one of the components results in less ketone formation. In all cases, when the reaction is run at 70 °C in either THF or dioxane, only the alcohol product **159** is obtained. The addition of water as a cosolvent results in no reaction.

Scheme 49[a]



[a] (a) transmetallation; (b) carbonyl insertion in to Rh−Ar bond; (c) hydrolytic cleavage of rhodium alkkoxide; (d) transmetallation; (e) β-H elimination

The mechanism for the production of the diaryl ketone products is likely the same as that observed by Hartwig in his stoichiometric studies of aryl rhodium additions to aldehydes (section 3.3.2). As outlined in Scheme 49, production of the diarylmethanol products arises from either protonation or transmetalation of the rhodium alkoxide **151**. Since these reactions are run under anhydrous conditions, the silanediol could be acting as the proton source. At 100 °C, β-hydride elimination becomes competitive, which will give the ketone and produce a rhodium-hydride. The pathway by which the Rh−H re-enters the catalytic cycle under these conditions is not known.

4.3 Reactions with Unactivated Alkenes and Alkynes

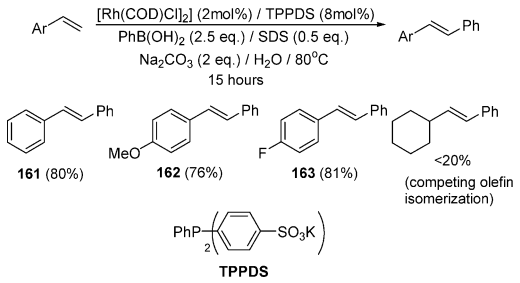
The stereoselective addition of carbon functionalities to unactivated alkenes and alkynes is a significant challenge in organic chemistry. Perhaps the best known reactions are those based on the palladium-catalyzed Heck reaction which employs aryl and alkenyl halides or sulfonates as organic electrophiles. Alternatively, alkenyl organometallics can be generated via hydroboration[97] or titanium catalyzed hydrozincation of alkynes[98] which can subsequently be cross-coupled with organohalides and sulfonates to generate a net C,H-addition to the alkyne in a two-step sequence. Rhodium has also recently found application in these reactions. In many of the rhodium-catalyzed processes, it is the ability of the rhodium−carbon bond to undergo protonolysis that creates a viable catalytic cycle. What emerges is a mode of catalytic activity that is unique among transition metals in the addition of organometallics to unactivated alkenes and alkynes.

4.3.1 Addition to Alkenes

We have shown that rhodium will catalyze the cross-coupling of styrenes with arylboronic acids to give *trans*-stilbenes in good yield.[59] For example, reaction of styrene with 2.5 equiv of $PhB(OH)_2$ and catalytic $[Rh(COD)Cl]_2$ and TPPDS (Rh:L ratio 1:2) in the presence of SDS and sodium carbonate in neat water at 80 °C gives stilbene **161** in 80% isolated yield (Scheme 50). A variety of aromatic alkenes reacted analogously as illustrated by the formation of 4-methoxy and 4-fluoro stilbenes **162** and **163**. Aliphatic alkenes give much lower yields.

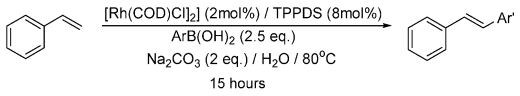
While SDS is not required in all cases, its use results in better reproducibility. In cases where the

Scheme 50



arylboronic acid contains a polar functionality, the use of SDS is essential to obtain good yield. With 4-$MeOC_6H_4B(OH)_2$, for example, addition of SDS results in an increase in yield from 22 to 69% (Scheme 51, entry 2). A similar increase was observed

Scheme 51

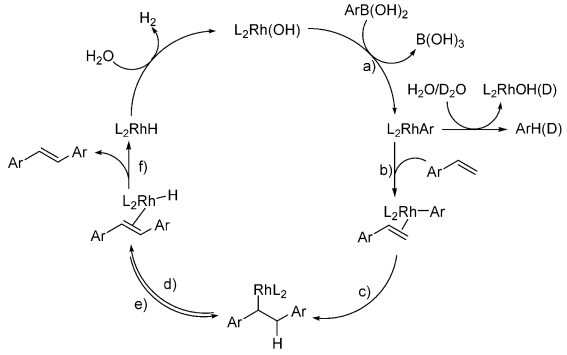


Entry	Arylboronic Acid	Yield (%) No SDS	0.5 eq. SDS
1	Phenyl	77	80
2	4-Methoxyphenyl	22	69
3	3-Methoxyphenyl	10	85
4	4-Acetylphenyl	<20	95

for the electron-deficient 4-$CH_3COCH_6H_4B(OH)_2$ (entry 4). In both these cases, it was determined that rhodium-catalyzed hydrolytic deboronation of the arylboronic acid was a significant side reaction.

Our proposed mechanism for these couplings is outlined in Scheme 52. Transmetalation of the aryl-

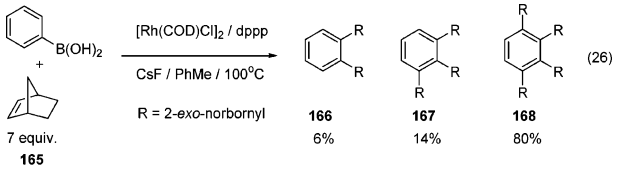
Scheme 52[a]



[a] (a) transmetallation; (b) alkene coordination; (c) olefin insertion into the Rh−C bond; (d) β-hydride elimination; (e) insertion of the olefin into the Rh−H bond; (f) ejection of the alkene.

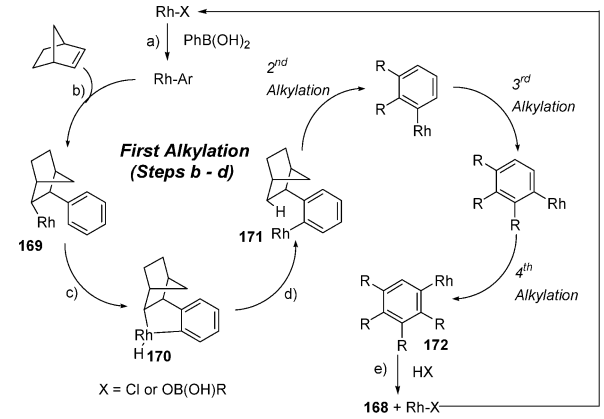
boronic acid will generate the aryl rhodium species that can undergo two possible reactions. Hydrolysis of the Rh−C bond will regenerate the rhodium hydroxide catalyst and consume the boronic acid. Alternatively, styrene will bind to the metal allowing for insertion of the alkene into the Rh−C bond. It is at this point in the cycle that the SDS may come into play. Since the rhodium is bound to water-soluble phosphorus ligands, the aryl rhodium complex will be situated predominantly in the water phase and undergo rapid hydrolysis in the absence of alkene. The SDS could serve to increase the concentration of styrene in the aqueous phase making cross-coupling competitive to the protolytic cleavage of the rhodium−carbon bond. After insertion of the alkene has occurred, β-hydride elimination will produce a rhodium hydride species and the stilbene product. It is important to note that neither the arylboronic acid nor the styrene is acting as a sacrificial hydride acceptor in contrast to the reactions reported by Mori[74] where the alkene is proposed to serve in this role. We favor hydrolysis of the Rh−H bond to produce dihydrogen and the Rh−OH catalyst in analogy to the same process that occurs with Rh−Ar bonds.[99]

An intriguing multiple alkylation (merry-go-round) reaction of aromatic rings has recently been reported by Miura, which involves the insertion of a strained alkene into a rhodium−aryl bond as a key step.[100] In a typical experiment, phenylboronic acid is reacted with 7 equiv of norbornene **165**, 2 equiv of cesium fluoride, and a catalyst prepared from $[Rh(COD)Cl]_2$ and dppp in toluene at 100 °C. A mixture of three products is formed where the tetra-alkylated arene **168** is isolated as the major product in 80% yield (eq 26).



The mechanism proposed by Miura is outlined in Scheme 53. Initial transmetalation (perhaps facili-

Scheme 53[a]



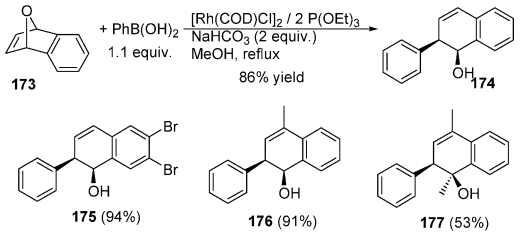
[a] (a) transmetallation; (b) carorhodation; (c) *ortho* C−H oxidative insertion; (d) reductive elimination; (e) hydrolytic derhodation

tated by the CsF) generates the rhodium phenyl complex that then coordinates to the *exo*-face of **165**. Insertion of the alkene into the Rh−C bond generates **169**. Since no β-hydrogens are present, cyclorhodation becomes the predominant pathway. *Ortho* C−H insertion generates **170** followed by reductive elimination to give a monoalkylated aryl rhodium complex **171**. This process will occur up to three more times to generate the tetraalkylated aryl rhodium complex **172**. At this point, the steric bulk of the arene is proposed to block further insertion of norbornene. Since no further transformations can occur, protonolysis by a boronic acid will occur to liberate **168** and regenerate the rhodium catalyst. This mecha-

nism illustrates the delicate balance that must occur between the competing rates of insertion and protonation of the organorhodium intermediates in many of the reactions described in this review.

Murakami has demonstrated that rhodium will catalyze the addition of aryl and alkenyl boronic acids to a variety of oxabenzonorbornadienes.[101] The best results were obtained with a catalyst prepared from mixing $[Rh(COD)Cl]_2$ with 2 equiv of $P(OEt)_3$. For example, reaction of **173** with 1.1 equiv of phenylboronic acid, the rhodium catalyst, and 2 equiv of $NaHCO_3$ in refluxing methanol gives **174** in 86% yield (Scheme 54). Similar results were obtained with

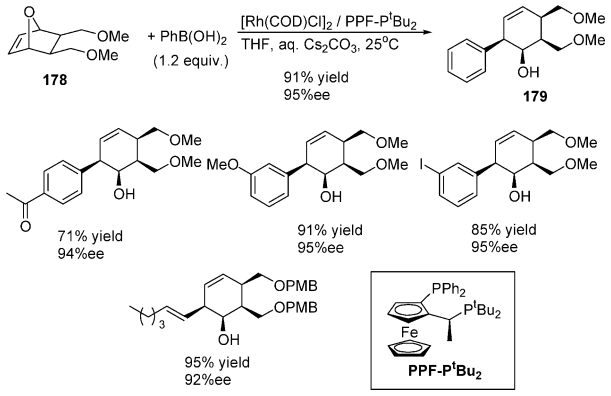
Scheme 54



substituted oxabenzonorbornadienes. Bromine atoms on the aromatic ring are tolerated in the generation of **175** and nonsymmetrical substrates react with high diastereoselectivity as exemplified in the formation of **176**. When two bridgehead methyl groups are present, **177** is produced in lower yield.

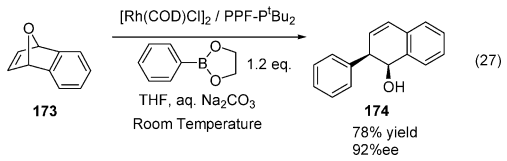
We have reported that this reaction can be carried out enantioselectively under different conditions.[102] For example, treatment of **178** with a slight excess of phenylboronic acid (1.2 equiv), aqueous cesium carbonate, and a catalyst generated from $[Rh(COD)Cl]_2$ and the chiral ligand PPF-P^{t}Bu$_2$ in THF at room temperature produces **179** in 91% yield and 95% ee as a single isomer. A variety of aryl and alkenylboronic acids are compatible, including electron-rich and electron-deficient species as well as arylboronic acids bearing an aryliodide functionality (Scheme 55).

Scheme 55

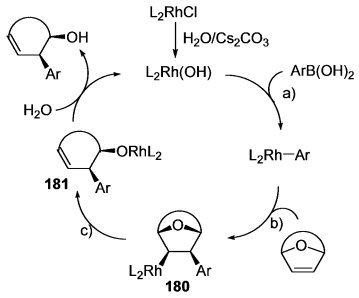


The optimal conditions for reaction of **178** generate a complex mixture of products when the more reactive **173** is used. In this case, changing to phenylboronic ethyleneglycol ester generates **174** in 78% yield and 92% ee (eq 27).

Murakami and Lautens independently suggested that the mechanism for these ring opening reactions commences with the formation of the arylrhodium(I) complex which coordinates the oxabicycle from the sterically more accessible *exo*-face (Scheme 56).



Scheme 56[a]



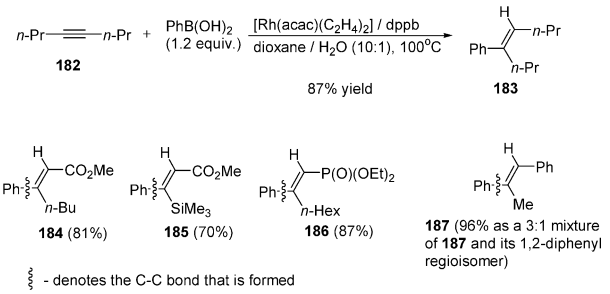
[a] (a) transmetallation; (b) enantioselective carborhodation; (c) β-oxy-elimination; (d) hydrolysis.

Insertion of the alkene into the carbon–rhodium bond generates alkyl–rhodium(I) complex **180**. While complex **180** closely resembles intermediate **170** in Miura's merry-go-round alkylation reactions, no products arising from *ortho* C–H insertion were observed. Instead, the exclusive mode of reaction is a β-oxygen elimination which regenerates the olefin and produces an alkoxyrhodium species **181**. Hydrolysis of **181** will liberate the product and regenerate the Rh(OH) catalyst.

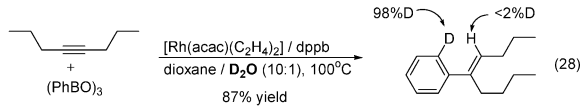
4.3.2 Addition to Alkynes

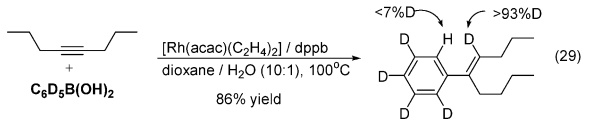
Hayashi has described a rhodium-catalyzed hydroarylation reaction of internal alkynes that gives trisubstituted alkenes in high yield and >20:1 *E*-selectivity.[103] For example, reaction of 4-octyne **182** with 1.2 equiv of $PhB(OH)_2$ in a 10:1 dioxane/water mixture at 100 °C with a catalyst prepared from $[Rh(acac)(C_2H_4)_2]$ and dppp generates (*E*)-4-phenyl-4-octene **183** in 87% yield and >20:1 selectivity (Scheme 57). By increasing the amount of phenylboronic acid to 5 equiv, the yield can be increased to 95%. When the alkyne is substituted with an electron withdrawing group such as an ester or a phosphonate, high regioselecitivties are observed for addition of the aryl group to the β-position as observed with **184**, **185**, and **186**. In the absence of an electron withdrawing group, unsymmetrically substituted alkynes give mixtures of regioisomers **187**.

Scheme 57



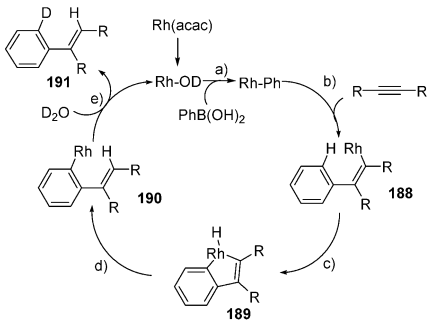
When these reactions are run in the presence of D_2O (which should produce a product with an alkene deuterium), deuterium-labeling occurs predominantly at an *ortho* position on the adjacent phenyl ring, *not* at the vinylic position (eq 28). Analogously, when phenylboronic-d_5 acid is used, a 1,4-deuterium shift occurs to give the vinylic deuterated alkene (eq 29).





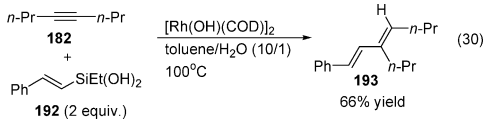
The (*E*)-selectivity and the 1,4-hydrogen(deuterium) shift have been rationalized by Hayashi via the mechanism described in Scheme 58. *Syn*-carborhodation of the alkyne with the arylrhodium(I) species generates the vinylrhodium complex **188** which undergoes *ortho* C−H insertion on the adjacant phenyl ring producing the rhodium(III) complex **189**. Subsequent reductive elimination of the alkene and hydride ligand produces the vinylic C−H bond and a new aryl−rhodium species **190**. Hydrolysis of **190** gives **191** and regenerates the catalyst. A closer examination of the potential side reactions in the catalytic cycle reveals a delicate balance that is required to give **191** as the sole product. While **188** could undergo 1,4-migration, hydrolysis or reaction with another alkyne, only the migration occurs. Similarly, **190** undergoes selective protonation instead of reacting with a second alkyne.

Scheme 58[a]

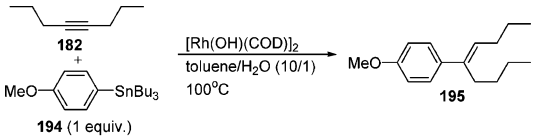


[a] (a) transmetallation; (b) alkyne coordination and carborhodation; (c) C-H insertion; (d) reductive elimination; (e) hydrolysis.

Mori has investigated the hydroarylation and alkenylation of alkynes with silanediols and found that they occur with $[Rh(COD)(OH)]_2$ as the catalyst in a toluene/water mixture (10:1) at 100 °C. These reactions generate the arylalkene and 1,3-diene products in moderate yield and high stereoselectivity. For example, treatment of **182** with vinyl silane **192** gives 1,3-diene **193** in 66% yield (eq 30).[104]



Scheme 59

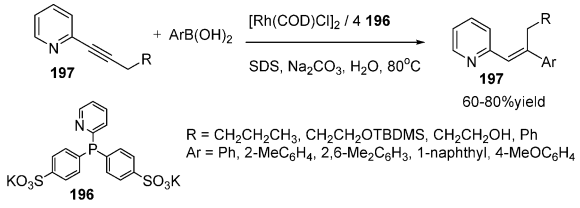


Entry	Additive (equiv.)	Time (h)	Yield
1	none	4	<5
2	Et_3SiOH (3)	4	40
3	$iPr_2Si(OH)_2$ (3)	13	48
4	$BuB(OH)_2$ (3)	13	40
5	PhOH (1)	14	72
6	$PhCO_2H$ (1)	14	trace

While a wide range of aryl silanediols could be coupled under these conditions, the corresponding reaction with tributyl(4-methoxylphenyl)stannane **194** and alkyne **182** resulted in less than 5% yield (Scheme 59, entry 1). To overcome this poor reactivity, the effect of protic additives was examined and it was determined that silanols, silanediols, and boronic acids all promote the reaction (entries 2−4).[104] The use of phenol gave the best results, providing **195** in 72% yield (entry 5). In contrast, benzoic acid failed to give **195**. The success of these protic additives may be a result of the fine balance between the reaction pathways described in Scheme 58 for the hydroarylation of alkynes. For example, if protonolysis of **190** does not occur at a sufficient rate, oligomerization by reaction with other alkynes may become competitive. Alternatively, in the absence of an additive, protonolysis of **188** or **190** may be too slow even in the presence of water as a cosolvent to permit efficient catalyst turnover. When arylboronic acid or silanediol nucleophiles are employed, the hydroxyl groups on these components may protonate the intermediate carbon−rhodium bond. The ability of these additives to induce reaction may be a result of their increased acidity compared to water. Alternatively, they may better be able to oxidatively add to rhodium(I). The failure of benzoic acid to induce reaction is likely a result of η^2-binding to rhodium. It is known that rhodium hydroxyl complexes will react with 1 equiv of benzoic acid to give the rhodium-(η^2-benzoate) complex[61] which may be unable to undergo transmetalation.

Lautens and Yoshida has shown that a pyridyl functionality can exert a dramatic directing effect in the hydroarylation of alkynes.[105] The optimal results were obtained using a catalyst prepared by mixing $[Rh(COD)Cl]_2$ and the pyridylphosphine ligand **196** (Rh:P = 1:2). For example, treatment of a variety of 2-alkynylpyridines **197** with 2.5−5.0 equiv of the arylboronic acid in the presence of Na_2CO_3 and SDS in neat water at 80°C produces the trisubstituted alkenes **198** as a single regio- and stereoisomer in 60−80% yield (Scheme 60). The ability of the pyridyl

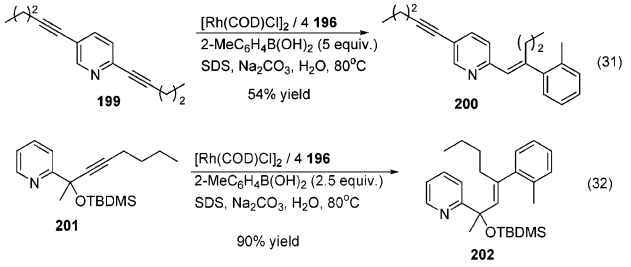
Scheme 60



group to direct the regioselectivity is illustrated by comparing these results to those obtained by Hayashi and Mori (vide supra) where a mixure of regioisomers is produced in the absence of an ester or phosphonate electron withdrawing group.

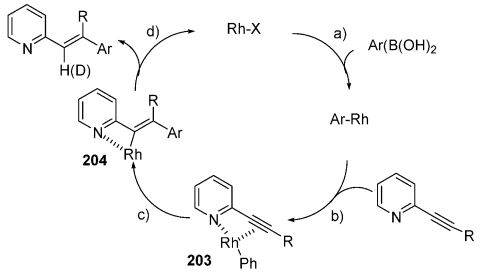
While both 4-alkenyl and 2-alkenylpyridines react in rhodium catalyzed 1,4-additions, the same is not observed with alkynylpyridines. No reaction is observed with 3-alkynyl and 4-alkynylpyridine, indicating that the nitrogen functionality must be situated adjacent to the alkyne for reaction to occur.

The importance of close proximity of the nitrogen functionality to the alkyne is further illustrated by the reaction of 2,5-bis(alkynyl)pyridine **199** where the addition of 2-tolylboronic acid occurs chemoselectively to the alkyne situated at the 2-position to give **200** (eq 31). Furthermore, the alkyne need not be directly connected to the pyridine ring for reaction to occur. For example, reaction of **201** gives **202** as the sole regio- and stereoisomer in 90% yield arising from delivery of the aryl group to the alkyne distal to the pyridyl group (eq 32).



The directing influence of the pyridyl group is illustrated in Scheme 61. Generation of the aryl

Scheme 61[a]

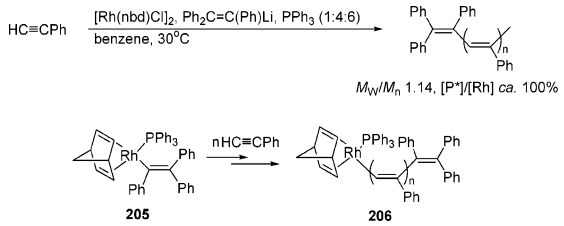


[a] (a) transmetallation; (b) bidentate substrate binding; (c) pyridyl-directed carborhodation; (d) hydro(deutero)lytic derhodation.

rhodium(I) species and binding of the alkyne will result in complex **203** where both the alkyne and the pyridyl group are coordinated. This binding mode will result in the delivery of the aryl group to the distal alkyne carbon and formation of alkenyl rhodium complex **204**. Protonolysis will liberate the product and regenerate the rhodium catalyst. In contrast to the deuterium-labeling studies by Hayashi where a 1,4-shift was observed, deuterium-labeling occurs exclusively at the vinylic position with alkynylpyridines.

The catalytic hydroarylation reactions described above are closely related to acetylene polymerization reactions that are catalyzed by similar rhodium complexes. For example, Masuda has reported that

Scheme 62



alkenyl rhodium(I) complexes will catalyze the living polymerization of phenylacetylene to give end-functionalized polymers (Scheme 62).[106] The initiator was determined to be the rhodium complex **205**. Given the intermediacy of **205** and **206** in these reactions and their resemblance to the vinylic rhodium intermediates in hydroarylation reactions, it seems likely that polymerization of the type described here is responsible for low yields in some hydroarylation reactions. The aryl analogue of **205** has also been demonstrated to effectively initiate the polymerization of aryl isocyanides.[107]

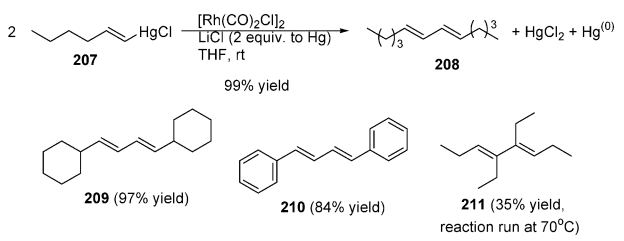
4.4 Formation of Biaryls, 1,3-Alkenes and Carbonyl Compounds

In the 100 years since the discovery of the Ullmann reaction, many transition metals have been found to catalyze the formation of alkene−alkene and aryl−aryl bonds in a highly efficient manner.[108] Among the most notable are the palladium-catalyzed reactions, including the Suzuki, Stille, and related processes. By simply exposing the cross-coupling partners to an atmosphere of carbon monoxide during the reaction, CO insertion products can be isolated. While the analogous rhodium-catalyzed reactions have been known for almost 30 years, they have not been subjected to the same level of intense study as the palladium systems and so have likely not had their full potential realized.

4.4.1 Organomercurial Reagents

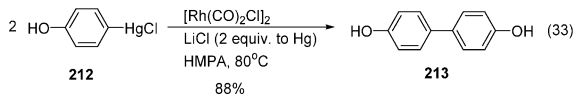
In 1977, Larock reported that rhodium(I) complexes catalyze the dimerization of vinyl- and arylmercurials.[109] Optimal catalysts were determined to be $[Rh(CO)_2Cl]_2$ or $RhCl_3 \cdot 3H_2O$ in the presence of excess lithium chloride. For example, treatment of 1-hexenylmercuric chloride **207** with catalytic $[Rh(CO)_2Cl]_2$ and 2 equiv of LiCl in THF at room temperature gives (*E*,*E*)-5,7-dodecadiene **208** in 99% yield (Scheme 63). These conditions were found to be

Scheme 63



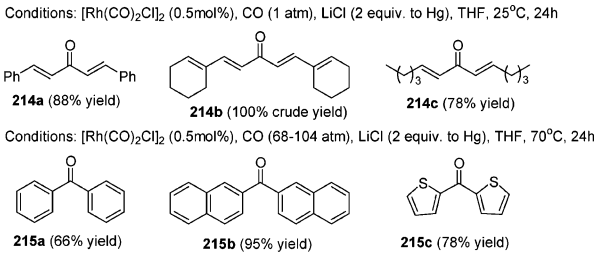
general for a wide range of vinylmercurials, **209** and **210**. Internal alkenylmercury salts require elevated temperature and result in lower yields, e.g. **211**.

The formation of biaryl compounds from arylmercurials requires more forcing conditions such as elevated temperatures and polar solvents such as acetonitrile and HMPA. Under these conditions, a variety or biaryls can be formed, including those containing free hydroxyl groups. For example, treatment of 4-hydroxyphenylmercuric chloride **212** with catalytic $[Rh(CO)_2Cl]_2$, 2 equiv of LiCl in HMPA at 80 °C gives **213** in 88% yield (eq 33).



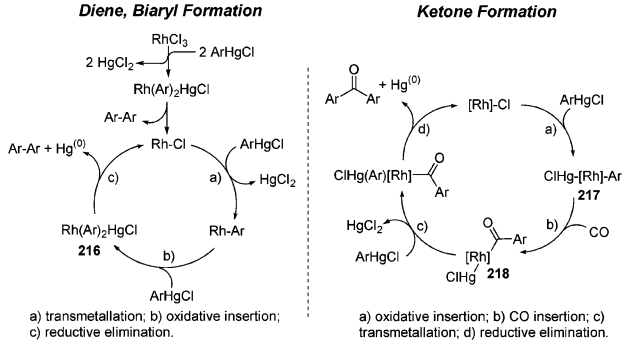
Heck and Larock found that using a CO atmosphere results in the formation of diaryl or divinyl ketones.[110,111] As with the formation of 1,3-dienes and biaryls, the homocoupling of arylmercurials requires more forcing conditions than the vinylmercurials. For example, divinyl ketones **214a**−**c** can be formed in good yield by reacting the vinylmerucuric chloride with catalytic $[Rh(CO)_2Cl]_2$ and 2 equiv of LiCl under one atmosphere of CO in THF at room temperature. To form the corresponding diaryl ketones **215a**−**c**, 68 to 104 atm of CO are required and the reaction must be heated to 70 °C (Scheme 64).

Scheme 64



While there is little direct evidence on which to base a mechanistic pathway, Larock favors a process in which the organomercurial can both transmetalate and oxidatively add to rhodium as illustrated in the diene/biaryl formation pathway (Scheme 65). Commencing with a rhodium(I) chloride species, transmetalation of ArHgCl will generate the aryl rhodium(I) species and $HgCl_2$. This complex can then oxidatively insert into the mercury carbon bond to generate biaryl rhodium(III) species **216**. Reductive elimination of Ar−Ar and mercury(0) will regenerate the active RhCl catalyst. The proposal that oxidative addition of organomercurials occurs across the Hg−C bond has precedent in stoichiometric processes.[112] While this proposal is sound, a different order of events cannot be ruled out. For example, oxidative addition of ArHgCl to the RhCl catalyst followed by transmetalation of another ArHgCl will generate the same biaryl rhodium(III) complex **216**.

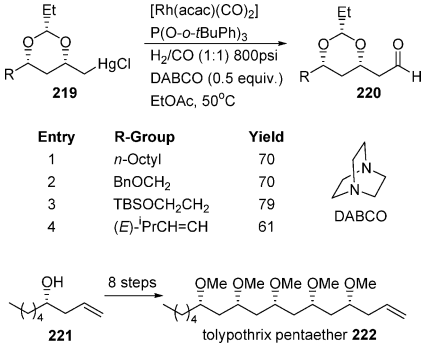
Scheme 65



Larock proposes a similar catalytic cycle for the formation of the ketone products (Scheme 65, Ketone Formation). In this case, an initial oxidative addition of the organomercurial generates **217** followed by coordination and insertion of CO into the rhodium−aryl bond to give the benzoylrhodium complex **218**. Transmetalation with another ArHgCl and concomitant reductive elimination of the ketone and mercury(0) regenerates the catalyst and completes the catalytic cycle. Again, no direct evidence was available to indicate whether oxidative addition or transmetalation was occurring first in the catalytic cycle.

Leighton has recently reported that rhodium catalyzes the formylation of organomercurials and applied this methodology to the synthesis of a naturally occurring polyether.[113] For example, treatment of the alcohol derived hemiacetal organomercurial **219** with a catalyst generated from $[Rh(acac)(CO)_2]$ and P(O-*ortho*-^{t}BuPh) under an atmosphere of H_2 and CO (1:1, 800 psi) in ethyl acetate generates aldehyde **220** in low yield. Subsequent experiments revealed that 0.5 equiv of DABCO as an additive was essential for high yields. In the presence of DABCO, a variety of hemiacetal organomercurials react to generate the corresponding aldehydes in 60 to 79% yield (Scheme 66). Iterative application of this methodology to homoallyl alcohol **221** was used to prepare the tolypothrix polyether **222** in eight steps. While the mechanism of these transformations is not clear, Leighton notes that once transmetalation or insertion of the rhodium catalyst with the organomercurial has occurred, a catalytic cycle similar to hydroformylation can be envisioned.

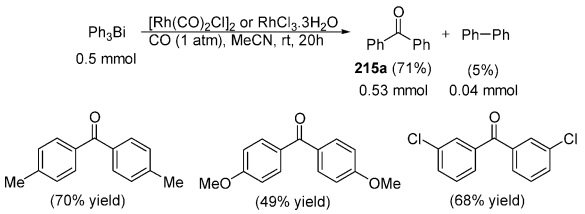
Scheme 66



4.4.2 Organobismuth Reagents

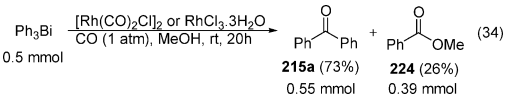
Uemura has demonstrated that rhodium will catalyze the carbonylation of triarylbismuth compounds to generate diaryl ketones in good yield.[114,115] Optimal conditions for ketone formation employ either $[Rh(CO)_2Cl]_2$ or $RhCl_3 \cdot 3H_2O$ as the catalyst in acetonitrile under one atmosphere CO at room temperature (Scheme 67). In most cases, formation of the biaryl compound **223** was a competing process. All three aryl groups of the triarylbismuthane are transferred

Scheme 67



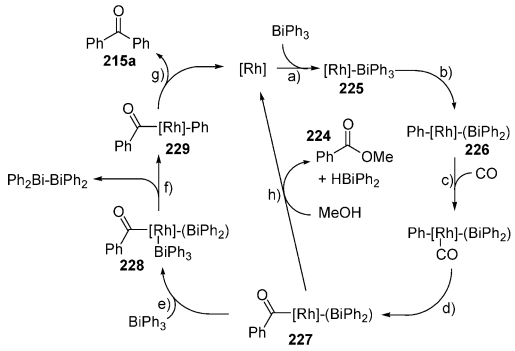
to provide the ketones in 50 to 70% yield (based on the aryl groups). When $RhCl_3 \cdot 3H_2O$ is used, reduction to rhodium(I) most likely occurs, either by a mechanism similar to that described in Scheme 65 above, or by the presence of the CO atmosphere.[116]

When these reactions are run in methanol, esters are formed in addition to ketones. For example, reaction of Ph_3Bi with a rhodium catalyst under a CO atmosphere in methanol at room temperature generates ketone **215a** in 73% yield and methylbenzoate **224** in 26% yield. Under these conditions, no biaryl byproduct is produced (eq 34).



Uemura proposes the catalytic cycle described in Scheme 68. Initial coordination of Ph_3Bi (Bi lies in

Scheme 68[a]



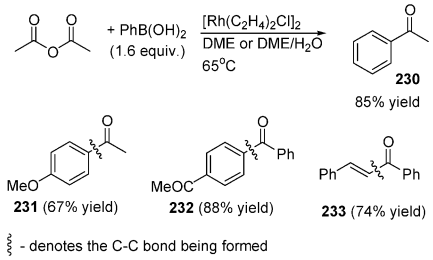
[a] (a) coordination of $BiPh_3$, (b) oxidative insertion of the Bi–Ph bond, (c) CO coordination, (d) insertion of CO into the Rh–Ph bond, (e) coordination of $BiPh_3$, (f) transmetallation with loss of dibismuthane, (g) reductive elimination of acyl and phenyl groups, (h) methanolysis.

the same group as phosphorus) to the rhodium catalyst produces complex **225**. This initial coordination is supported experimentally by the poisoning effects of triarylphosphines which preferentially bind to the rhodium and prevent the formation of **225**. In analogy to the many oxidative addition reactions of bound triarylphosphines to low valent metals,[117] insertion of rhodium into a Ph–Bi bond produces **226**. Coordination of CO and subsequent migratory insertion into the rhodium–phenyl bond gives benzoylrhodium complex **227**. In acetonitrile as the solvent, another Ph_3Bi will coordinate to the metal giving **228** which undergoes a transmetalation process to give the rhodium(III) species **229** and $Ph_2Bi–BiPh_2$. Evidence for a second triarylbismuth compound binding and delivering the phenyl group to the rhodium was obtained by carrying out crossover experiments. When two different Ar_3Bi are reacted simultaneously, a mixture of the two homoaryl ketones and the heteroaryl ketone is produced indicating that the delivery of the second aryl group is an intermolecular process and does not originate from the Ph_2Bi ligand already bound to the rhodium. Reductive elimination of the acyl and aryl ligands on **229** then occurs to produce ketone **215a** and regenerate the catalyst. In methanol as the solvent, intermediate **227** undergoes competitive methanolysis to give the methylester **224** and the rhodium catalyst. The ability of triarylbithmuth compounds to both oxidatively add and to transmetalate has also been observed in catalytic systems involving palladium.[118]

4.4.3 Organoboron Reagents

Frost has recently shown that rhodium can be used to catalyze the addition of aryl- and alkenylboronic acids to anhydrides giving ketones in high yield.[119] For example, heating a solution of acetic anhydride, 1.6 equiv of $PhB(OH)_2$ and catalytic $[Rh(ethylene)_2Cl]_2$ in DME or a DME/water mixture in a sealed tube gives benzophenone **230** in 85% yield (Scheme 69).

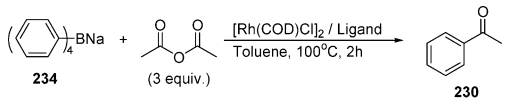
Scheme 69



A variety of organoboronic acids can be employed, including electron-rich arenes **231**, electron-deficient arenes **232**, and alkenes **233**.

Miura has reported a similar reaction with tetraarylborates and anhydrides.[120] In this case, the addition of phosphine ligands was found to exert a beneficial influence on the reaction outcome. For example, treatment of **234** with 3 equiv of acetic anhydride in the presence of a catalyst generated by mixing $[Rh(COD)Cl]_2$ and a phosphine ligand in toluene at 100 °C for 2 h gives acetophenone **230** in variable yield (Scheme 70). Use of sterically hindered

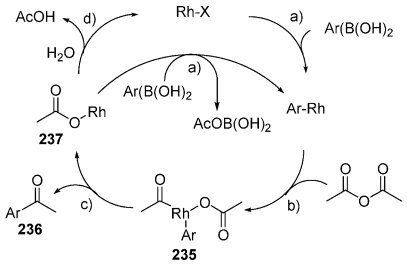
Scheme 70



Entry	Ligand	Yield
1	PPh_3	51
2	P^tBu_3	79
3	dppf	91
4	dppp	133

and electron-rich phosphines such as P^tBu_3 gives **230** in 79% yield (entry 2), whereas less electron-rich phosphines, such as PPh_3, give lower yields (entry 1). Bidentate phosphines can also be used (entries 3 and 4). The best result was obtained with dppp which gives **230** in 133% yield based on **234** indicating that more than one phenyl group can be transferred (entry 4).

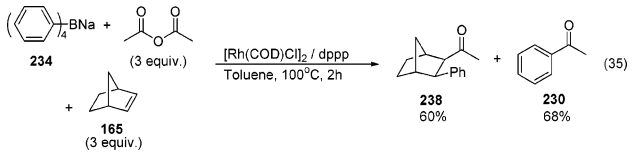
Scheme 71[a]



[a] (a) transmetallation; (b) oxidative insertion into the anhydride C−O bond; (c) reductive elimination; (d) hydrolysis.

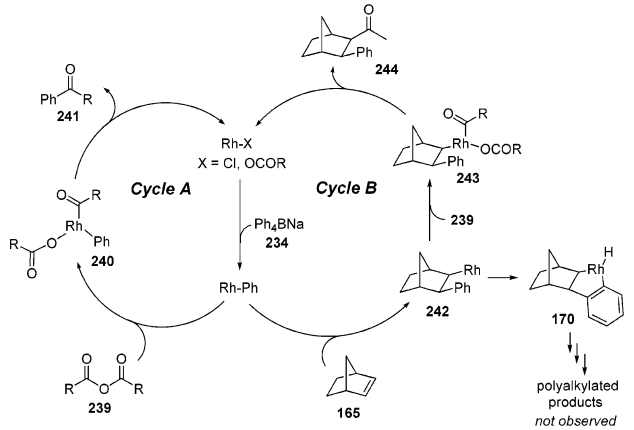
A plausible catalytic cycle is outlined in Scheme 71. Transmetalation of the arylboronic acid to the rhodium(I) catalyst generates the aryl rhodium(I) species. Oxidative addition of the anhydride across the C−O bond generates rhodium(III) species **235** and subsequent reductive elimination of the acyl and aryl groups produces the ketone **236** and a rhodium acetate complex **237**. Under anhydrous conditions, transmetalation to **237** could occur to regenerate the Rh−Ar complex directly. In aqueous solvents, **237** could be hydrolyzed to give the rhodium hydroxide catalyst.

Miura has also reported a three-component coupling reaction.[120] By reacting Ph_4BNa **234**, acetic anhydride and norbornene **165** with a catalyst prepared from $[Rh(COD)Cl]_2$ and dppp in toluene at 100 °C, a mixture of the two component product **230** and the three component product **238** is obtained (eq 35). While rhodium has been shown to react with arylboronic acids and **165** to produce polyalkylated arenes (section 3.3.1), no such products could be detected in these three-component coupling reactions.



The mechanism for the production of **238** and **230** is outlined in Scheme 72. Miura proposes the pres-

Scheme 72



ence of two catalytic cycles. Thus, the transmetalation of Ph_4BNa **234** with the Rh−X complex generates the aryl rhodium(I) species that can react in two ways. Oxidative insertion of the anhydride **239** can occur to give the arylacylrhodium(III) complex **240** which will reductively eliminate the ketone product **241** and regenerate the catalyst (cycle A). Conversely, insertion of the norbornyl alkene into the rhodium−phenyl bond will produce a new alkylrhodium(I) complex **242** (cycle B). Subsequent oxidative addition of the anhydride generates the rhodium(III) complex **243** which can reductively eliminate the three-component product **244** and regenerate the catalyst. While **242** has been shown to react via *ortho*-C−H insertion to give **170**, this process was not observed in these reactions.

5. Outlook

Since the seminal report by Miyaura in 1997, significant advances have been made in the area of carbon−carbon bond forming reactions of organometallics with rhodium catalysts. High yielding reactions with a variety of substrate classes have been established, including highly enantioselective versions. Of particular interest is the ability to perform these reactions in the presence of water, either as a cosolvent or as the exclusive reaction medium, which makes this field of research very promising from an environmental point-of-view. Importantly, many of the reactions show complementary modes of reactivity when compared to the more highly studied and understood palladium systems. The continued efforts of those involved will likely lead to rhodium catalysts playing an important role in the field of carbon−carbon bond forming reactions.

6. Acknowledgment

We thank NSERC, the ORDCF, and the University of Toronto for valuable support of out research programs. K.F. would like to thank NSERC for postgraduate scholarships.

7. Abbreviations

Acac = acetylacetate
AcacH = acetylacetone
Dppb = 1,4-bis(diphenylphosphino)butane
Dppp = 1,3-bis(diphenylphosphino)propane
Dppf = bis(diphenylphosphino)ferrocene
COD = 1,5-cyclooctadiene
COE = cyclooctene
DME = 1,2-dimethoxyethane
SDS = sodium dodecyl sulfate
TPPDS = triphenyphosphinodisulfonate
BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
THF = tetrahyrofuran
TFP = trifurylphosphine
Dppe = 1,2-bis(diphenylphosphino)ethane
Tht = tetrahydrothiophene
DABCO = 1,4-diazabicyclo[2.2.2]ocatane

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